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Statin use and clinical outcomes in older men: a prospective population-based study

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ABSTRACT

Objective: The aim of this analysis was to investigate the relationship of statins with institutionalisation and death in older men living in the community, accounting for frailty.

Design: Prospective cohort study.

Setting: Community-dwelling men participating in the Concord Health and Ageing in Men Project, Sydney, Australia.

Participants: Men aged ≥70 years (n=1665).

Measurements: Data collected during baseline assessments and follow-up (maximum of 6.79 years) were obtained. Information regarding statin use was captured at baseline, between 2005 and 2007. Proportional hazards regression analysis was conducted to estimate the risk of institutionalisation and death according to statin use (exposure, duration and dose) and frailty status, with adjustment for socio-demographics, medical diagnosis, and other clinically relevant factors. A secondary analysis used propensity score matching to replicate covariate adjustment in regression models.

Results: At baseline, 43% of participants reported taking statins. Over 6.79 years of follow-up, 132 (7.9%) participants were institutionalised and 358 (21.5%) participants had died. In the adjusted models, baseline statin use was not statistically associated with increased risk of institutionalisation (hazard ratio [HR] =1.60; 95% confidence intervals [CI]SS: 0.98 to 2.63) or death (HR=0.88; 95%CI: 0.66 to 1.18). There was no significant association between duration or dose of statins used with either outcome. Propensity scoring yielded similar findings. Compared to non-frail participants not prescribed statins, the adjusted HR for institutionalisation for non-frail participants prescribed statins was 1.43 (0.81to 2.51), for frail participants not prescribed statins was 2.07 (1.11to 3.86) and for frail participants prescribed statins was 4.34 (2.02 to 9.33).

Conclusions: These data imply no independent association between statin use and institutionalisation or death in older men. These findings call for real-world trials specifically designed for older frail people to examine the impact of statins on clinical outcomes.

ARTICLE SUMMARY

Article focus

- Evidence from randomised trials support the benefits of statins in reducing cardiovascular morbidity and mortality.
- There is limited data in relation to statin use and clinical outcomes in representative populations of community-dwelling older people.

Key messages

- The findings of this prospective cohort study imply no independent association between statin use and institutionalisation or death in community-dwelling older men.
- Frail men were more likely to be institutionalised and die than non-frail men, independent of their statin exposure.
- Randomised trials in frail and robust older people with clinically relevant endpoints are required to inform therapy in this population.

Strengths and limitations of this study

- This is a large prospective cohort study of community-dwelling older men, with rich data sources.
- The study sample comprised older men living in a defined geographical location, which may limit the study's generalisability.
- Although we have attempted to limit potential confounding by adjusting our analysis for clinically important covariates, the possibility of confounding by indication and unmeasured confounders cannot be excluded.

INTRODUCTION

Statins or 3-hydroxy-3-methylglutaryl (HMG) coenzyme A reductase inhibitors are commonly used medicines in older people. In a Canadian population aged ≥65 years, 42% were identified as statin users.[1] A recent Australian study reported 43% of community-dwelling people aged ≥75 years using statins.[2] The benefits of statins in relation to primary and secondary prevention of cardiovascular morbidity and mortality have been demonstrated in a number of randomised clinical trials (RCTs). [3 4] However, it is not clear how the findings of these trials translate to clinically significant outcomes in general populations of older people. This may be because the representation and representativeness of older people in published RCTs of statins is generally poor.[5] Therefore, observational studies are often essential to elucidate the intended effects of medicines in this population.[6] Moreover, the benefit to harm ratio of medicines is altered in older adults due to co-morbid conditions, age-related physiological changes, increased risk of adverse drug reactions and multiple medicines.[7]

The pharmacological response to medicines is further altered when older individuals become frail.[8] Frailty is a geriatric syndrome associated with functional impairment and increased vulnerability to disease, disability, and mortality in older people.[9] Frail individuals are more likely to use more medicines,[10] and are at increased risk of adverse effects from medicines. Conversely, frail older people are less likely to be recruited to and participate in RCTs.[8] There are currently limited data to guide prescribing to minimise medication-related harms in older people with geriatric syndromes including frailty. Moreover, evidence on clinically relevant outcomes of Drug-Geriatric Syndrome Interactions (DGSI) in older adults who have already developed a geriatric syndrome is limited.[11] It is unknown whether medicines do more good than harm in older adults with established geriatric syndromes.

There have been mixed findings across observational studies investigating the associations between statin use and geriatric syndromes and physical performance measures in older people. Statins have been associated with faster walking speed in patients with peripheral arterial or vascular disease.[12 13] In contrast, a recent study reported no association of statin use with mobility in older community-dwelling people.[14] In a study of community-dwelling older disabled women, current statin use was not associated with incident frailty over three years.[15] Statins in older people may increase the risk of both institutionalisation and death by causing myopathy or muscle damage.[16] Recent evidence also suggests that statins have adverse effects of energy and fatigue with exertion.[17] Statin-related myopathy is likely to have a greater impact in frail older adults with limited musculoskeletal reserve than in younger people who generally have more muscle mass and strength.

While the data from published RCTs and prospective studies indicate that statins reduce the incidence of cardiovascular events and all-cause mortality,[18] there are still significant gaps in evidence on the safety of statins in a real-world setting. To our knowledge, no study has examined the association between the use of statins and institutionalisation in a representative population of older people, or in frail older people. Moreover, the evidence on the impact of interactions between statins and frailty (DGSI) on clinical outcomes in older people is yet to be established. The objectives of this study were to investigate the relationship of statin use, and of interactions between statins and frailty with institutionalisation and death in community-dwelling older men living in Sydney, Australia.

METHODS

Study population

Participants were community-dwelling men enrolled in the Concord Health and Ageing in Men Project (CHAMP), Sydney, Australia.[19] Eligible participants were ≥70 years and living in a specific study area. The only exclusion criterion was living in a residential aged care facility (RACF). The Electoral Roll was chosen as the sampling frame for the study. In Australia, registration on the Electoral Roll is compulsory and regularly updated, making it a suitable population-wide sampling frame. Men were recruited during 2005-2007. Of the 2815 eligible men contacted, 1511 (53.7%) participated in the study. An additional 194 (11.4%) men living in the study area heard about the study from friends or the local media and were recruited before receiving an invitation letter, giving a final sample of 1705 participants. Participants underwent baseline assessments which comprised self-completed study questionnaires and a clinical assessment that consisted of physical performance measures, neuropsychological testing, biological measures and medication inventory. Participants also agreed to be contacted every two years subsequently for follow-up assessment. After exclusion for missing data (n=40), a total of 1665 men were included in the analysis (Figure 1).

Medication assessment and classification of statin exposure

A medication inventory was conducted on each participant by trained personnel during the baseline clinic visit. Participants were instructed to bring all prescription and over-the-counter medications they were taking to the clinic visit for review. Participants were asked whether they had taken any subsidised prescription or non-prescription medications during the past month. Details of all medications and prescription pattern were recorded. Reported medicines were coded using the Iowa Drug Information Service code numbers.

Statin exposure was defined using three approaches. We categorised participants as “statin users” versus “non-users”. Data on the duration of statin use (years) were obtained and participants were dichotomised at the upper quartile (≤3 versus ≥4). Statin users were characterised using the units of equivalent dose, indicating potency for lipid-lowering effect from clinical trials.[20 21] The daily dose of each statin was converted to an equivalent statin dose based on a lipid-lowering effect of 10mg of atorvastatin (equivalent to 5mg of rosuvastatin, 20mg of simvastatin, 40mg of lovastatin, 40mg of pravastatin, and 80mg of fluvastatin). Statin users were grouped into three categories, based on the data distribution, as receiving a low (equivalent dose < 2), medium (equivalent dose 2-4), and high (equivalent dose ≥4) statin dose.

Study outcomes

Data on institutionalisation and death were regularly updated by telephone contact with the participants or their nominated contact person at 4-monthly intervals. Men who were not contactable by telephone were sent letters at four monthly intervals. Institutionalisation was defined as entry into a nursing home facility or hostel at any time during the follow-up period of 6.79 years. In Australia, there are two main forms of RACFs: low-level care facilities (hostels) and high-level care facilities (nursing homes). Self-care retirement villages are not considered to be RACFs and residents are not considered “institutionalised”. Moreover, institutionalisation in Australia is nearly always permanent rather than short-term admission for rehabilitative care after surgery or medical illness. For death outcome, if men withdrew from the study but agreed to passive follow up, the New South Wales *Registry of Births, Deaths and Marriages* was contacted to ascertain any deaths. Follow-up began at the baseline assessment and ended on the date of death or the end of the study period. For withdrawals, the end date was the date at which the contact with the death registry was made.

Covariates

Data on clinically relevant covariates that may influence the association between statin use and outcomes were obtained.[14 15] Demographic variables included age, education, and marital status. Data on country of birth were obtained and participants were categorised as Australian-born, overseas-born from an English-Speaking background (ESB), and overseas-born from a non-ESB. For those who consumed at least 12 alcoholic drinks in the past year, the frequency and quantity of alcohol consumption was assessed, and men were categorised as safe drinkers (1-21 alcoholic drinks per week) or harmful drinkers (>21 alcoholic drinks per week). Participants who were current non-drinkers were characterised as either "lifelong abstainers" or "ex-drinkers". Tobacco smoking status (allocated as "never smoker", "ex-smoker" or "current smoker") was also assessed.

Data on the cardiovascular diseases (CVD) including hypertension, coronary artery disease or myocardial infarction, angina, and congestive heart failure were obtained, and dichotomised at the upper quartile (≤1 versus ≥2). Other medical conditions included: diabetes, thyroid dysfunction, osteoporosis, Paget's disease, stroke, Parkinson's disease, epilepsy, intermittent claudication, chronic obstructive lung disease, liver disease, chronic kidney disease or renal failure, cancer (excluding non-melanoma skin cancers), or arthritis. The number of reported comorbidities was dichotomised at the upper quartile (≤1 versus ≥2). Data on body mass index (BMI; kg/m^2) was obtained. Multiple medication use or polypharmacy was defined as the use of ≥5 regular prescription medicines.[22] Corrected visual acuity was assessed using a Bailey-Lovie chart (<6/19 indicating poor vision).[23] Data on self-rated health were obtained and dichotomised into excellent/good versus fair/poor/very poor. Depressive symptoms were assessed with the 15-item Geriatric Depression Scale (≥ 5 indicative of depressive symptoms).[24] Blood samples were drawn after overnight fasting. Total cholesterol, high density lipoprotein (HDL) cholesterol, and triglyceride concentrations were obtained and analysed as continuous variables.

All participants were screened for cognitive impairment, and those who tested positive underwent full neuropsychological assessment. Participants were classified as cognitively impaired if they were diagnosed with either dementia or mild cognitive impairment.[25] Functional status was measured with Activities of Daily Living (ADL) and Instrumental Activities of Daily (IADL) scales. Disability in ADL and IADL was defined as needing help with ≥1 activities.[26 27] Frailty in this population, described in detail elsewhere[28 29] was defined according to the criteria used in the Cardiovascular Health Study (CHS): weight loss/shrinking, weakness, exhaustion, slowness and low activity.[9] For the weakness and slowness components, the same criteria as in the CHS were applied. Adapted criteria were used for weight loss, exhaustion and low activity as the exact measurements used in the CHS were not available in this study.[28 29] Participants were considered *frail* if they had three or more frailty criteria, intermediate (*pre-frail*) with one or two criteria and robust (*not-frail*) without any criteria.

Statistical Analysis

Data are summarised as means (standard deviations) or counts (proportions). Differences between statin users and non-users were compared using the non-parametric or χ^2-tests as appropriate. Univariate analyses of the association between the various study measures and outcomes were conducted using Log-rank tests and examination of survival curves. Tests for linear trends were performed for continuous variables to determine the linearity of their relationship with institutionalisation and death, and to determine whether to enter these variables into models as continuous or categorical variables. The appropriate parameterisation of continuous variables as either categorical or continuous was also confirmed in the final model by using Akaike's Information Criterion (AIC). Univariate Cox regressions were conducted to determine the unadjusted hazard ratios (HR) with 95% confidence intervals (CI) for the effects of statins on institutionalisation and death. We then conducted the Cox proportional hazards regression models for the effects of statins on institutionalisation and death, adjusted for all potential confounding factors at baseline. These analyses were performed for all different categorises of statin exposure.

The propensity score analysis was performed to minimize the effects of covariates in the evaluation of the association between statin use and institutionalisation and death.[30] Participant-specific propensity scores were estimated from a logistic regression model to predict the probability of statin prescription. All covariates were considered in the logistic regression model. The association between statins and institutionalisation and death was evaluated in Cox regressions models after adjusting for the estimated propensity score as a continuous and stratified (grouped into quintile) variable. Moreover, as older individuals with geriatric syndromes may have higher risk for either institutionalisation or death we conducted subgroup analysis. We stratified participants based on frailty status and statin use as *robust* or *pre-frail not on statins*; *robust* or *pre-frail on statins*; *frail not on statins* and *frail on statins*. Robust or pre-frail participants are referred as "non-frail" in the analysis. We also tested for interaction to assess whether statin effects differed in frail and non-frail men. Data were analysed using SAS version 9.3 (SAS Institute Inc., Cary, North Carolina). The Kaplan-

Meier survival curves were generated using SPSS software version 19.0 (SPPS Inc, Chicago, Illinois).

RESULTS

The baseline characteristics according to statin use are presented in Table 1. The mean (SD) age of participants was 79.6 (5.5) years. At baseline, 743 (42.9%) participants were identified as taking a statin. Statin users were younger (p=0.04), had more CVD comorbidities (p<0.0001), used more medications (p<0.0001), had higher BMI (p<0.0001), and were less likely to report *good* or *excellent health* (p=0.003).In this population, 17% of participants reported taking statins for ≤3 years, and 26% for ≥4 years. In relation to the statin dose, 17% were taking low statin doses, 15% medium doses and 10% high statin doses. Over 6.79 years of follow-up, 132 (7.9%) participants were institutionalised and 358 (21.5%) participants had died. Figure 2 shows the Kaplan-Meier survival curves for institutionalisation and death according to reported statin exposure and frailty status at baseline. There was a significant difference between the groups in time to institutionalisation or death.

Table 2 summarises the results of the Cox regression models. In the adjusted models, baseline use of statins was not significantly associated with increased risks of institutionalisation (HR=1.60; 95%CI: 0.98 to 2.63) or death (HR=0.88; 95%CI: 0.66 to 1.18). Medium (HR=2.00; 95%CI: 1.02 to 3.93) and high (HR=2.45; 95%CI: 1.12 to 5.33) dose statin users were significantly more likely to be institutionalised when compared to those not taking statins. There was no association between the duration or dose of statins and death. The propensity score adjusted HR were not significantly altered apart from the association of statin doses with institutionalisation (table 3). In the propensity score adjusted models, current use of statins was not significantly associated with institutionalisation (HR=1.43; 95%CI: 0.87 to 2.34) or death (HR=0.82; 95%CI: 0.61to 1.10). Medium or high dose statin use was not significantly associated with a higher risk of institutionalisation compared to non-users.

The HRs for institutionalisation and death in frail versus non-frail men according to statin use are presented in Table 4. Using non-frail men who were not taking statins as the reference group at baseline, non-frail men prescribed statins had an adjusted HR of 1.43 (95%CI: 0.81 to 2.51) for institutionalisation, frail participants not taking statins had an adjusted HR of 2.07 (95%CI: 1.11to 3.86) and frail participants prescribed statins had a HR of 4.34 (95%CI: 2.02 to 9.33) for institutionalisation. Frail participants prescribed statins had a HR of 1.24 (95%CI: 0.71to 2.17) for death compared to non-frail participants not prescribed statins. However, among men not using statins, frail participants had a HR of 1.53 (95%CI: 1.03 to 2.28) for mortality compared to non-frail participants. In the adjusted models, there was no significant interaction between frailty and statin use with respect to institutionalisation (p=0.40) or mortality (p=0.73).

DISCUSSION

The objective of this cohort analysis was to evaluate the relationship between statins and two clinically important outcomes, institutionalisation and death in older men, accounting for frailty. The main finding of this prospective observational study of community-dwelling older men is the lack of independent association between the use of statins and institutionalisation or death. However, in this population, frailty was associated with higher risks of institutionalisation and death. Frail men were approximately two times more likely to be institutionalised and die over 6.8 years of follow-up compared to non-frail men, regardless of their medication exposure.

The prevalence of statin use in this population is comparable to recent studies[1 2] but much higher than that reported in studies of older people recruited in 1990s. In a study of older disabled women in the US, recruited during 1993-1998,[15] the prevalence of statin use was 8.4% compared to 12.9% in a community-dwelling sample of older people enrolled in the Health Ageing and Body Composition study during 1997-1998.[14] There are no studies conducted in older people that have investigated the association of statin use with institutionalisation. Some studies have showed that statins improve physical function, walking speed [12] but do not lower risk of incident frailty over 3 years.[15] Better performance on functional measures is protective against institutionalisation and death.[31 32] Moreover, frailty has been associated with an increased risk of institutionalisation[33] and death.[34] In this sample, frail men were more likely to be institutionalised and die than non-frail men, irrespective of their statin exposure. These findings suggest that statins in frail older men may not reduce the risk of institutionalisation or death.

There are several strengths of this study including the prospective design, good quality medication and outcome data, and adjustment for a number of covariates related to the risk of institutionalisation and death. Frailty was ascertained using the validated scale.[35] We also performed sensitivity analysis including propensity score analysis and stratification of statin users according to their frailty status. While there are different propensity score models that can be used to balance measured covariates, the covariate propensity score adjustment has the best performance for estimating relative risks.[36]

However, there are important limitations to this study. The possibility of confounding by indication and unmeasured confounders needs to be acknowledged, as with any other observational study. Participants with CVDs would be more likely to be prescribed statins and among those with CVDs, those with more CVDs and more severe CVDs would be even more likely to be prescribed statins. In addition, participants adherent to treatment are likely to do better, which is hard to capture. These characteristics may have over or under estimated the HRs. In relation to statin exposure, non-users group may include former users of statins. The possibility of recall bias should be considered as the assessment of CVD comorbidities and other diseases was based on self-report alone. The modified measurements for three components of the frailty score were used in this sample. The study's generalisability may be limited as this sample comprised older men living in a defined geographical location. However, the response rate in the CHAMP study is similar to other comparable cohort studies of this type.[19] Moreover, the use of statins in this population (42.9%) was very similar to a random sample of older Australians aged ≥75 (43.0%). Finally, the findings of this study may not be applicable to older women.

In this prospective observational study, use of statins was not associated with increased risk of institutionalisation or death. However, in this sample, frail men were more likely to be institutionalised and die than non-frail men, independent of their statin exposure. Given the wide use of statins in older adults, regular clinical review of any observed or potential risks and benefits of statin therapy should be performed with older patients. Further longitudinal studies are warranted to confirm these associations in older women and in populations of older people across different settings. Finally, these findings call for pragmatic real-world trials specifically tailored for older frail people to examine the impact of statins on institutionalisation and other important clinical endpoints.

TABLES

Table 1. Characteristics of 1665 study participants according to baseline reported use of statins.

Characteristic#	Total (n=1665)	Statin users (n=712; 42.8%)	Non-users (n=953; 57.2%)	P-value
Age, mean (SD)	76.9 (5.5)	76.5 (5.1)	77.2 (5.7)	0.04
Age groups (years)				
<80	1184 (71.1)	533 (74.9)	651 (68.3)	
≥80	481 (28.9)	179 (25.1)	302 (31.7)	0.0004
Currently married	1255 (75.4)	550 (77.3)	705 (74.0)	0.13
Years of education, ≥7 years	1396 (84.7)	596 (84.5)	800 (84.8)	0.91
Country of birth				
Australia	831 (49.9)	356 (50.0)	475 (49.8)	
ESB immigrant	103 (6.2)	42 (5.9)	61 (6.4)	
Non-ESB immigrant	731 (43.9)	314 (44.1)	417 (43.8)	0.91
Alcohol consumption				

Lifelong non-drinker	144 (8.8)	53 (7.6)	91(9.8)	
Ex-drinker	239 (14.6)	105 (15.0)	134 (14.4)	
Safe drinker (1-21 drinks per week)	1127 (68.9)	492 (70.1)	635 (68.1)	
Harmful drinker (>21 drinks per week)	125 (7.7)	52 (7.4)	73 (7.8)	0.45
Smoking status				
Never smoker	620 (37.6)	240 (34.0)	380 (40.3)	
Previous smoker	929 (56.4)	431 (61.1)	498 (52.9)	
Current smoker	98 (6.0)	34 (4.8)	64 (6.8)	0.003
CVD diseases (≥2)	156 (9.5)	123 (17.4)	33 (3.5)	<0.0001
Self-reported comorbidities (≥2)	179 (10.9)	76 (10.8)	103 (10.9)	0.91
Polypharmacy (≥5)	618 (37.1)	412 (57.9)	206 (21.6)	<0.0001
Self-rated health, good or excellent	1153 (70.1)	463 (65.5)	690 (73.6)	0.0003
Visual acuity, low (<6/19)	71 (4.4)	18 (2.3)	53 (5.8)	0.002
BMI, mean (SD), kg/m^2	27.8 (4.0)	28.4 (3.7)	27.4 (4.2)	<0.0001
Depressive symptoms	240 (14.6)	100 (14.2)	140 (14.9)	0.70

Cognitive impairment (MCI or dementia)	205 (12.3)	76 (10.7)	129 (13.5)	0.08
ADL disability	134 (8.1)	50 (7.1)	84 (8.8)	0.19
IADL disability	674 (41.2)	318 (45.1)	356 (38.2)	0.005
Frail	147 (9.0)	53 (7.6)	94 (10.4)	0.08
Total cholesterol, mmol/L	4.6 (1.0)	4.0 (0.8)	5.0 (0.9)	<0.0001
HDL-cholesterol, mmol/L	1.4 (0.4)	1.4 (0.4)	1.5 (0.4)	0.0003
Triglycerides, mmol/L	1.4 (1.2)	1.4 (0.7)	1.4 (1.5)	0.06

Abbreviations: ADL, activities of daily living; BMI, body mass index; CVD, cardiovascular disease; ESB, English speaking background; HDL, high density lipoprotein; IADL, instrumental activities of daily living; MCI, mild cognitive impairment.

[#]Data are given as means (SD) or number (percentage). Percentages may not add up to 100% due to missing data.

Table 2. Association between reported statin use at baseline and institutionalisation and death

	Unadjusted HR (95%CI) (n=1665)		Adjusted HR (95%CI)[#] (n=1497)	
Categorisation of statin use	**Institutionalisation**	**Death**	**Institutionalisation**	**Death**
Statin exposure				
Non-users[*]	1.00	1.00	1.00	1.00
Users	0.90 (0.63, 1.27)	0.93 (0.75, 1.15)	1.60 (0.98, 2.63)	0.88 (0.66, 1.18)
Duration of statin use				
Non-users	1.00	1.00	1.00	1.00
0 - ≤3 years	1.10 (0.71, 1.68)	0.87 (0.65, 1.16)	1.73 (0.97, 3.10)	0.76 (0.53, 1.09)
≥4 years	0.73 (0.46, 1.17)	0.97 (0.75, 1.25)	1.48 (0.82, 2.68)	0.99 (0.71, 1.37)
Standardised daily dose[^]				
Non-users	1.00	1.00	1.00	1.00
Low	0.77 (0.47, 1.25)	0.98 (0.75, 1.29)	1.25 (0.69, 2.28)	0.92 (0.66, 1.29)
Medium	1.01 (0.61, 1.66)	0.97 (0.71, 1.33)	2.00 (1.02, 3.93)	0.95 (0.65, 1.40)
High	1.00 (0.55, 1.84)	0.73 (0.48, 1.12)	2.45 (1.12, 5.33)	0.65 (0.40, 1.07)

Abbreviations: CI, confidence intervals; HR, hazard ratio.

#Adjusted for age, education, marital status, alcohol use, smoking, body mass index, self-reported comorbidities, self-reported cardiovascular diseases, impaired vision, depression, cognitive impairment, functional status, self-rated health, polypharmacy and for total cholesterol, high density lipoprotein cholesterol and triglyceride concentrations.

*Non-users, the reference group.

^Standardised daily dose was defined as followed: one unit of equivalent dose was based on lipid-lowering effect of 10mg of atorvastatin (fluvastatin 80mg, lovastatin 40mg, pravastatin 40mg, simvastatin 2mg, rosuvastatin 5mg) (18,19). Low dose was defined as <2 standardised unit, medium dose as 2-4 standardised unit, and high dose as ≥4 standardised unit.

Table 3. Association between reported statin use at baseline and institutionalisation and death, adjusted for continuous and quintiles of propensity scores (n=1497)

	Adjusted HR (95%CI)[#]		Adjusted HR (95%CI)[*]	
Categorisation of statin use	**Institutionalisation**	**Death**	**Institutionalisation**	**Death**
Statin exposure				
Non-users[^]	1.00	1.00	1.00	1.00
Users	1.43 (0.87, 2.34)	0.82 (0.61, 1.10)	1.32 (0.81, 2.15)	0.81 (0.61, 1.08)
Duration of statin use				
Non-users	1.00	1.00	1.00	1.00
0 - ≤3	1.77 (1.01, 3.11)	0.74 (0.52, 1.06)	1.65 (0.95, 2.86)	0.73 (0.51, 1.04)
≥4	1.15 (0.64, 2.08)	0.88 (0.64, 1.22)	1.07 (0.59, 1.91)	0.87 (0.64, 1.20)
Standardised daily dose[†]				
Non-users	1.00	1.00	1.00	1.00
Low	1.17 (0.65, 2.13)	0.85 (0.61, 1.19)	1.10 (0.60, 1.99)	0.84 (0.60, 1.17)
Medium	1.73 (0.92, 3.27)	0.87 (0.60, 1.28)	1.57 (0.85, 2.93)	0.87 (0.60, 1.27)

High	1.71 (0.82, 3.57)	0.66 (0.41, 1.07)	1.56 (0.75, 3.24)	0.65 (0.41, 1.05)

Abbreviations: CI, confidence intervals; HR, hazard ratio.

[#]The HR estimated from Cox models, adjusted for continuous propensity score.

[*]The HR estimated from Cox models, adjusted for quintiles of propensity score.

[^]Non-users, the reference group.

[†]Standardised daily dose was defined as followed: one unit of equivalent dose was based on lipid-lowering effect of 10 mg of atorvastatin (fluvastatin 80mg, lovastatin 40mg, pravastatin 40mg, simvastatin 20mg, rosuvastatin 5mg) (18,19). Low dose was defined as <2 standardised unit, medium dose as 2-4 standardised unit, and high dose as ≥4 standardised unit.

Table 4. Association between reported statin use in frail versus non-frail men and institutionalisation and death

	Unadjusted HR (95%CI) (n=1631)	Adjusted HR (95%CI)[#] (n=1497)
Institutionalisation		
Non-frail participants not on statins[*]	1.00	1.00
Non-frail participants on statins	0.93 (0.60, 1.44)	1.43 (0.81, 2.51)
Frail participants not on statins	4.58 (2.82, 7.44)	2.07 (1.11, 3.86)
Frail participants on statins	5.47 (3.11, 9.61)	4.34 (2.02, 9.33)
Death		
Non-frail participants not on statins	1.00	1.00
Non-frail participants on statins	1.05 (0.83, 1.35)	0.90 (0.66, 1.23)
Frail participants not on statins	3.40 (2.49, 4.65)	1.53 (1.03, 2.28)
Frail participants on statins	3.01 (1.97, 4.61)	1.24 (0.71, 2.17)

Abbreviations: CI, confidence intervals; HR, hazard ratio.

[#]Adjusted for age, education, marital status, alcohol use, smoking, body mass index, self-reported comorbidities, self-reported cardiovascular diseases, impaired vision, depression, cognitive impairment, functional status, self-rated health, polypharmacy, total cholesterol, high density lipoprotein cholesterol and triglyceride concentrations.

[*]Non-users, the reference group.

FIGURES

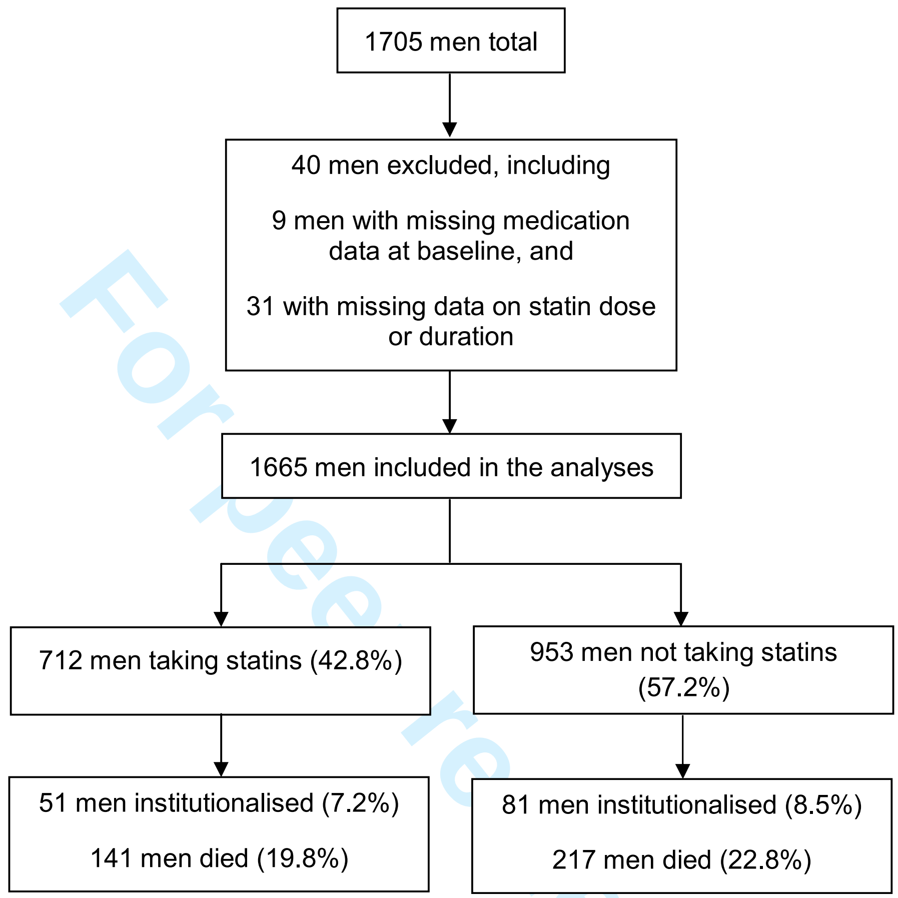
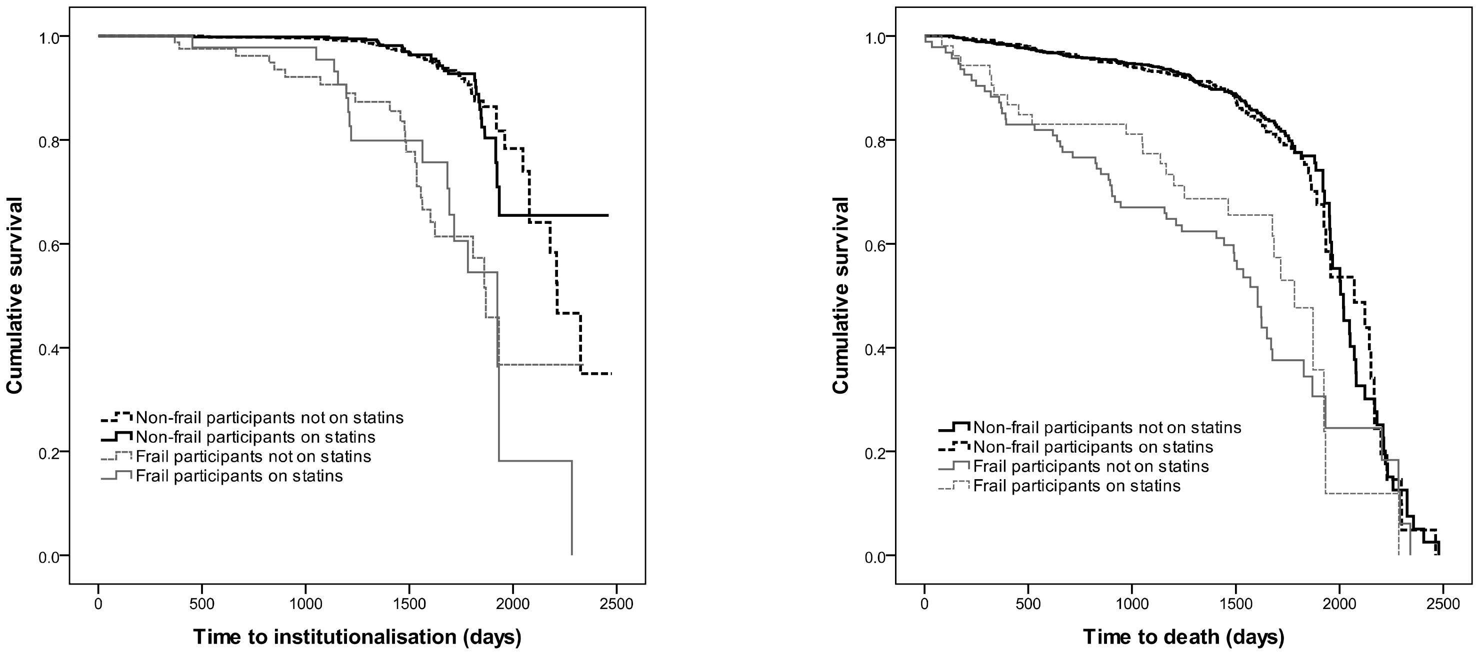


Figure 1. Flowchart for participants taking statins and institutionalisation and death in the CHAMP study



	Non-frail participants not on statins	Non-frail participants on statins	Frail participants not on statins	Frail participants on statins
N=1631	836	648	94	53
Institutionalised	50 (6.0%)	34 (5.3%)	25 (26.6%)	16 (30.2%)
Dead	149 (17.8)	115 (17.8%)	56 (59.6%)	25 (47.2%)

Figure 2. Kaplan-Meier survival curves for the time until institutionalisation (log-rank test, p<0.0001) and death (log-rank test, p<0.0001) by reported statin exposure and frailty.

Contributors

All authors contributed to the design of the study and co-wrote the manuscript. DG undertook the analysis and is the guarantor.

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Competing interests

None.

Ethical approval

The study was approved by the Sydney South West Area Health Service Human Research Ethics Committee Concord Repatriation General Hospital, Sydney, Australia.

Data sharing

No additional data available.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	8-9
Objectives	3	State specific objectives, including any prespecified hypotheses	9
Methods			
Study design	4	Present key elements of study design early in the paper	10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	10,11
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10-13
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*10-13*
Bias	9	Describe any efforts to address potential sources of bias	14
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10-13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	13-15
		(*b*) Describe any methods used to examine subgroups and interactions	14
		(*c*) Explain how missing data were addressed	10
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	14
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	16-17
		(b) Give reasons for non-participation at each stage	30
		(c) Consider use of a flow diagram	30
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	16
		(b) Indicate number of participants with missing data for each variable of interest	Tables 1-4
		(c) Summarise follow-up time (eg, average and total amount)	11, 16
Outcome data	15*	Report numbers of outcome events or summary measures over time	16, 30
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	16, 17
		(*b*) Report category boundaries when continuous variables were categorized	12, 13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Tables 3 and 4, pages 16, 17
Discussion			
Key results	18	Summarise key results with reference to study objectives	18
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	32

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Statin use and clinical outcomes in older men: a prospective population-based study

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Statin use and clinical outcomes in older men: a prospective population-based study

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Key words: statins, older people, outcomes, death, institutionalisation.

Word count: 3399

ABSTRACT

Objective: The aim of this analysis was to investigate the relationship of statins with institutionalisation and death in older men living in the community, accounting for frailty.

Design: Prospective cohort study.

Setting: Community-dwelling men participating in the Concord Health and Ageing in Men Project, Sydney, Australia.

Participants: Men aged ≥70 years (n=1665).

Measurements: Data collected during baseline assessments and follow-up (maximum of 6.79 years) were obtained. Information regarding statin use was captured at baseline, between 2005 and 2007. Proportional hazards regression analysis was conducted to estimate the risk of institutionalisation and death according to statin use (exposure, duration and dose) and frailty status, with adjustment for socio-demographics, medical diagnosis, and other clinically relevant factors. A secondary analysis used propensity score matching to replicate covariate adjustment in regression models.

Results: At baseline, 43% of participants reported taking statins. Over 6.79 years of follow-up, 132 (7.9%) participants were institutionalised and 358 (21.5%) participants had died. In the adjusted models, baseline statin use was not statistically associated with increased risk of institutionalisation (hazard ratio [HR] =1.60; 95% confidence intervals [CI]: 0.98 to 2.63) or death (HR=0.88; 95%CI: 0.66 to 1.18). There was no significant association between duration or dose of statins used with either outcome. Propensity scoring yielded similar findings. Compared to non-frail participants not prescribed statins, the adjusted HR for institutionalisation for non-frail participants prescribed statins was 1.43 (0.81to 2.51), for frail participants not prescribed statins was 2.07 (1.11to 3.86) and for frail participants prescribed statins was 4.34 (2.02 to 9.33).

Conclusions: These data suggest lack of significant association between statin use and institutionalisation or death in older men. These findings call for real-world trials specifically designed for older frail people to examine the impact of statins on clinical outcomes.

ARTICLE SUMMARY

Article focus

- Evidence from randomised trials support the benefits of statins in reducing cardiovascular morbidity and mortality.
- There is limited data in relation to statin use and clinical outcomes in representative populations of community-dwelling older people.

Key messages

- In this prospective cohort study there was not significant association between statin use and institutionalisation or death in community-dwelling older men.
- Frail men were more likely to be institutionalised and die than non-frail men, independent of their statin exposure.
- Randomised trials utilising operational frailty definitions with clinically relevant endpoints are required to inform therapy in this population.

Strengths and limitations of this study

- This is a prospective cohort study of community-dwelling older men, with rich data sources.
- The study may have been underpowered to demonstrate the statistical significance in relation to statin use and institutionalisation.
- Observational studies of preventative medication users, including statins, are often biased by healthy user and healthy tolerator bias.

INTRODUCTION

Statins or 3-hydroxy-3-methylglutaryl (HMG) coenzyme A reductase inhibitors are commonly used medicines in older people. In a recent Australian study 43% of community-dwelling people aged ≥75 years reported using statins.[1] The benefits of statins in relation to primary and secondary prevention of cardiovascular morbidity and mortality have been demonstrated in a number of randomised clinical trials (RCTs).[2 3] However, it is not clear how the findings of these trials translate to clinically significant outcomes in general populations of older people, as the representation and representativeness of older people in published RCTs of statins is generally poor.[4] Therefore, observational studies are often essential to elucidate the intended effects of medicines in this population.[5] Moreover, the benefit to harm ratio of medicines is altered in older adults due to co-morbid conditions, age-related physiological changes, increased risk of adverse drug reactions and multiple medicines.[6]

The pharmacological response to medicines is further altered when older individuals become frail.[7] Frailty is a geriatric syndrome associated with functional impairment and increased vulnerability to disease, disability, and mortality in older people.[8] Frail individuals are more likely to use more medicines,[9] and are at increased risk of adverse effects from medicines.[7] Conversely, frail older people are less likely to be recruited to and participate in RCTs.[7] There are currently limited data to guide prescribing to minimise medication-related harms in older people with geriatric syndromes including frailty. Moreover, evidence on clinically relevant outcomes of Drug-Geriatric Syndrome Interactions (DGSI) in older adults who have already developed a geriatric syndrome is limited.[10] It is unknown whether medicines do more good than harm in older adults with established geriatric syndromes.

There have been mixed findings across observational studies investigating the associations between statin use and geriatric syndromes and physical performance measures in older people. Statins have been associated with faster walking speed in patients with peripheral arterial or vascular disease.[11 12] In contrast, a recent study reported no association of statin use with mobility in older community-dwelling people.[13] In a study of community-dwelling older women, current statin use was not associated with incident frailty over three years.[14] Statins in older people may increase the risk of both institutionalisation and death by causing myopathy or muscle damage.[15] Recent evidence also suggests that statins have adverse effects of energy and fatigue with exertion.[16] Statin-related myopathy is likely to have a greater impact in frail older adults with limited musculoskeletal reserve than in younger people who generally have more muscle mass and strength.

While the data from published RCTs and prospective studies indicate that statins reduce the incidence of cardiovascular events,[17] there are still significant gaps in evidence on the safety of statins in a real-world setting. To our knowledge, no study has examined the association between the use of statins and institutionalisation in a representative population of older people, or in frail older people. Moreover, the evidence on the impact of interactions between statins and frailty (DGSI) on clinical outcomes in older people is yet to be established. The objectives of this study were to investigate the relationship of statin use, and of interactions between statins and frailty with institutionalisation and death in community-dwelling older men living in Sydney, Australia.

METHODS

Study population

Participants were community-dwelling men enrolled in the Concord Health and Ageing in Men Project (CHAMP), Sydney, Australia.[18] Eligible participants were ≥70 years and living in a specific study area. The only exclusion criterion was living in a residential aged care facility (RACF). The Electoral Roll was chosen as the sampling frame for the study. In Australia, registration on the Electoral Roll is compulsory and regularly updated, making it a suitable population-wide sampling frame. Men were recruited during 2005-2007. Of the 2815 eligible men contacted, 1511 (53.7%) participated in the study. An additional 194 (11.4%) men living in the study area heard about the study from friends or the local media and were recruited before receiving an invitation letter, giving a final sample of 1705 participants. Participants underwent baseline assessments which comprised self-completed study questionnaires and a clinical assessment that consisted of physical performance measures, neuropsychological testing, biological measures and medication inventory. Participants also agreed to be contacted every two years subsequently for follow-up assessment. After exclusion for missing data (n=40), a total of 1665 men were included in the analysis (Figure 1).

Medication assessment and classification of statin exposure

A medication inventory was conducted on each participant by trained personnel during the baseline clinic visit. Participants were instructed to bring all prescription and over-the-counter medications they were taking to the clinic visit for review. Participants were asked whether they had taken any prescription or non-prescription medications during the past month. Details of all medications and prescription pattern were recorded. Reported medicines were coded using the Iowa Drug Information Service code numbers.

Statin baseline exposure was defined using three approaches. We categorised participants as “statin users” versus “non-users”. Data on the duration of statin use (years) were obtained and participants were dichotomised at the upper quartile (<4 versus ≥4). Statin users were characterised using the units of equivalent dose, indicating potency for lipid-lowering effect from clinical trials.[19 20] The daily dose of each statin was converted to an equivalent statin dose based on a lipid-lowering effect of 10mg of atorvastatin (equivalent to 5mg of rosuvastatin, 20mg of simvastatin, 40mg of lovastatin, 40mg of pravastatin, and 80mg of fluvastatin). Statin users were grouped into three categories, based on the data distribution, as receiving a low (equivalent dose < 2), medium (equivalent dose 2-4), and high (equivalent dose ≥4) statin dose.

Study outcomes

Data on institutionalisation and death were regularly updated by telephone contact with the participants or their nominated contact person at 4-monthly intervals. Men who were not contactable by telephone were sent letters at four monthly intervals. Institutionalisation was defined as entry into a nursing home facility or hostel at any time during the follow-up period of 6.79 years (average 4.0 years). In Australia, there are two main forms of RACFs: low-level care facilities (hostels) and high-level care facilities (nursing homes). Self-care retirement villages are not considered to be RACFs and residents are not considered “institutionalised”. Moreover, institutionalisation in Australia is nearly always permanent rather than short-term admission for rehabilitative care after surgery or medical illness. For death outcome, if men withdrew from the study but agreed to passive follow up, the New South Wales *Registry of Births, Deaths and Marriages* was contacted to ascertain any deaths. Follow-up began at the baseline assessment and ended on the date of death or the end of the study period. For withdrawals, the end date was the date at which the contact with the death registry was made.

Covariates

Data on clinically relevant covariates that may influence the association between statin use and outcomes were obtained.[13 14] Demographic variables included age, education, and marital status. Data on country of birth were obtained and participants were categorised as Australian-born, overseas-born from an English-Speaking background (ESB), and overseas-born from a non-ESB. For those who consumed at least 12 alcoholic drinks in the past year, the frequency and quantity of alcohol consumption was assessed, and men were categorised as safe drinkers (1-21 alcoholic drinks per week) or harmful drinkers (>21 alcoholic drinks per week). Participants who were current non-drinkers were characterised as either "lifelong abstainers" or "ex-drinkers". Tobacco smoking status (allocated as "never smoker", "ex-smoker" or "current smoker") was also assessed.

Data on the cardiovascular diseases (CVD) including hypertension, coronary artery disease or myocardial infarction, angina, and congestive heart failure were obtained. The number of CVD diseases was dichotomised at the upper quartile (≤1 versus ≥2). Other medical conditions included: diabetes, thyroid dysfunction, osteoporosis, Paget's disease, stroke, Parkinson's disease, epilepsy, intermittent claudication, chronic obstructive lung disease, liver disease, chronic kidney disease or renal failure, cancer (excluding non-melanoma skin cancers), or arthritis. The number of reported comorbidities was dichotomised at the upper quartile (≤1 versus ≥2). Data on body mass index (BMI; kg/m^2) was obtained. Multiple medication use or polypharmacy was defined as the use of ≥5 regular prescription medicines.[21] Corrected visual acuity was assessed using a Bailey-Lovie chart (<6/19 indicating poor vision).[22] Data on self-rated health were obtained and dichotomised into excellent/good versus fair/poor/very poor. Depressive symptoms were assessed with the 15-item Geriatric Depression Scale (≥ 5 indicative of depressive symptoms).[23] Blood samples were drawn after overnight fasting. Total cholesterol, high density lipoprotein (HDL) cholesterol, and triglyceride concentrations were obtained and analysed as continuous variables.

All participants were screened for cognitive impairment, and those who tested positive underwent full neuropsychological assessment. Participants were classified as cognitively impaired if they were diagnosed with either dementia or mild cognitive impairment.[24] Functional status was measured with Activities of Daily Living (ADL) and Instrumental Activities of Daily (IADL) scales. Disability in ADL and IADL was defined as needing help with ≥1 activities.[25 26] Frailty in this population, described in detail elsewhere[27 28] was defined according to the criteria used in the Cardiovascular Health Study (CHS): weight loss/shrinking, weakness, exhaustion, slowness and low activity.[8] For the weakness and slowness components, the same criteria as in the CHS were applied. Adapted criteria were used for weight loss, exhaustion and low activity as the exact measurements used in the CHS were not available in this study.[27 28] Participants were considered *frail* if they had three or more frailty criteria, intermediate (*pre-frail*) with one or two criteria and robust (*not-frail*) without any criteria.

Statistical Analysis

Data are summarised as means (standard deviations) or counts (proportions). Differences in baseline characteristics between statin users and non-users were compared using the non-parametric or χ^2-tests as appropriate. Univariate analyses of the association between the various study measures and outcomes were conducted using Log-rank tests and examination of survival curves. Tests for linear trends were performed for continuous variables to determine the linearity of their relationship with institutionalisation and death, and to determine whether to enter these variables into models as continuous or categorical variables. The appropriate parameterisation of continuous variables as either categorical or continuous was also confirmed in the final model by using Akaike's Information Criterion (AIC). Univariate Cox regressions were conducted to determine the unadjusted hazard ratios (HR) with 95% confidence intervals (CI) for the effects of statins on institutionalisation and death. We then conducted the Cox proportional hazards regression models for the effects of statins on institutionalisation and death, adjusted for all potential confounding factors at baseline including age, education, marital status, alcohol use, smoking, BMI, self-reported comorbidities, self-reported cardiovascular diseases, impaired vision, depression, cognitive impairment, functional status, self-rated health, polypharmacy, total cholesterol, high density lipoprotein cholesterol and triglyceride concentrations. These analyses were performed for all different categorises of statin exposure.

The propensity score analysis was performed to minimize the effects of covariates in the evaluation of the association between statin use and institutionalisation and death.[29] Participant-specific propensity scores were estimated from a logistic regression model to predict the probability of statin prescription. All covariates were considered in the logistic regression model. The association between statins and institutionalisation and death was evaluated in Cox regressions models after adjusting for the estimated propensity score as a continuous and stratified (grouped into quintile) variable. Moreover, as older individuals with geriatric syndromes may have higher risk for either institutionalisation or death we conducted subgroup analysis. We stratified participants based on frailty status and statin use as *robust* or *pre-frail not on statins*; *robust* or *pre-frail on statins*; *frail not on statins* and *frail on statins*. Robust or pre-frail participants are referred as "non-frail" in the analysis. We also tested for interaction to assess whether statin effects differed in frail and non-frail men. Data were analysed using SAS version 9.3 (SAS Institute Inc., Cary, North Carolina). The Kaplan-Meier survival curves were generated using SPSS software version 19.0 (SPPS Inc, Chicago, Illinois).

RESULTS

The baseline characteristics according to statin use are presented in Table 1. The mean (SD) age of participants was 79.6 (5.5) years. At baseline, 743 (42.9%) participants were identified as taking a statin. Statin users were younger (p=0.04), had more CVD comorbidities (p<0.0001), used more medications (p<0.0001), had higher BMI (p<0.0001), and were less likely to report *good* or *excellent health* (p=0.003).In this population, 17% of participants reported taking statins for <4 years, and 26% for ≥4 years. In relation to the statin dose, 17% were taking low statin doses, 15% medium doses and 10% high statin doses. Over 6.79 years of follow-up, 132 (7.9%) participants were institutionalised and 358 (21.5%) participants had died. Figure 2 shows the Kaplan-Meier survival curves for institutionalisation and death according to reported statin exposure and frailty status at baseline. There was a significant difference between the groups in time to institutionalisation or death.

Table 2 summarises the results of the Cox regression models. In the adjusted models, baseline use of statins was not significantly associated with increased risks of institutionalisation (HR=1.60; 95%CI: 0.98 to 2.63) or death (HR=0.88; 95%CI: 0.66 to 1.18). Medium (HR=2.00; 95%CI: 1.02 to 3.93) and high (HR=2.45; 95%CI: 1.12 to 5.33) dose statin users were significantly more likely to be institutionalised when compared to those not taking statins. There was no association between the duration or dose of statins and death. The propensity score adjusted HR were not significantly altered apart from the association of statin doses with institutionalisation (table 3). In the propensity score adjusted models, current use of statins was not significantly associated with institutionalisation (HR=1.43; 95%CI: 0.87 to 2.34) or death (HR=0.82; 95%CI: 0.61to 1.10). Medium or high dose statin use was not significantly associated with a higher risk of institutionalisation compared to non-users.

The HRs for institutionalisation and death in frail versus non-frail men according to statin use are presented in Table 4. Using non-frail men who were not taking statins as the reference group at baseline, non-frail men prescribed statins had an adjusted HR of 1.43 (95%CI: 0.81 to 2.51) for institutionalisation, frail participants not taking statins had an adjusted HR of 2.07 (95%CI: 1.11to 3.86) and frail participants prescribed statins had a HR of 4.34 (95%CI: 2.02 to 9.33) for institutionalisation. Frail participants prescribed statins had a HR of 1.24 (95%CI: 0.71to 2.17) for death compared to non-frail participants not prescribed statins. However, among men not using statins, frail participants had a HR of 1.53 (95%CI: 1.03 to 2.28) for mortality compared to non-frail participants. In the adjusted models, there was no significant interaction between frailty and statin use with respect to institutionalisation (p=0.40) or mortality (p=0.73).

DISCUSSION

The objective of this cohort analysis was to evaluate the relationship between statins and two clinically important outcomes, institutionalisation and death in older men, accounting for frailty. The main finding of this prospective observational study of community-dwelling older men is the lack of independent association between the use of statins and institutionalisation or death. However, in this population, frailty was associated with higher risks of institutionalisation and death. Frail men were approximately two times more likely to be institutionalised and die over 6.8 years of follow-up compared to non-frail men, regardless of their medication exposure.

The prevalence of statin use in this population is comparable to recent studies[1 30] but much higher than that reported in studies of older people recruited in 1990s. In a study of older disabled women in the US, recruited during 1993-1998,[14] the prevalence of statin use was 8.4% compared to 12.9% in a community-dwelling sample of older people enrolled in the Health Ageing and Body Composition study during 1997-1998.[13] There are no studies conducted in older people that have investigated the association of statin use with institutionalisation. Some studies have showed that statins improve physical function, walking speed [11] but do not lower risk of incident frailty over 3 years.[14] Better performance on functional measures is protective against institutionalisation and death.[31 32] In our study, statin users had a hazard ratio of 1.60 (95% CI: 0.98 to 2.63) for increased risk of institutionalisation. Interestingly, high dose statin users had a hazard ratio of 2.45 (95% CI: 1.12 to 5.33) for increased risk of institutionalisation. However, this association was not significant in the propensity score adjusted model. Future studies conducted in larger populations are needed to investigate associations between statins and institutionalisation in older people. In relation to statins and mortality, among older people with diabetes living in the community, statin use has been associated with reduced risk of cardiovascular and all-cause mortality.[33] In contrast, the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial data demonstrates benefits in reducing the risks of coronary diseases, however there are no benefits in overall mortality.[34]

Moreover, frailty has been associated with an increased risk of institutionalisation[35] and death.[36] In this sample, frail men were more likely to be institutionalised and die than non-frail men, irrespective of their statin exposure. Even though there was no significant interaction between statin use and frailty on institutionalisation rates, frail men using statins had twice the risk of institutionalisation as frail men not using statins. These findings suggest that statins in frail older men may not reduce the risk of institutionalisation or death. Studies with larger number of frail participants are needed to estimate the risks of statins in frail older people.

There are several strengths of this study including the prospective design, good quality medication and outcome data, and adjustment for a number of covariates related to the risk of institutionalisation and death. A careful and systematic medication inventory was performed by checking all medications brought in by the men during a clinic visit. Frailty was ascertained using the validated scale.[37] We also performed sensitivity analysis including propensity score analysis and stratification of statin users according to their frailty status. While there are different propensity score models that can be used to balance measured covariates, the covariate propensity score adjustment has the best performance for estimating relative risks.[38]

However, there are important limitations to this study. The possibility of confounding by indication and unmeasured confounders needs to be acknowledged, as with any other observational study. Participants with CVDs would be more likely to be prescribed statins and among those with CVDs, those with more CVDs and more severe CVDs would be even more likely to be prescribed statins. In addition, participants adherent to treatment are likely to do better, which is hard to capture. These characteristics may have over or under estimated the HRs. The implications of healthy user bias (eg. unhealthy individuals will be less likely to use statins, which may indicate benefits of statins in observational studies) and healthy tolerator bias (eg. adherence to preventative drugs including statins is associated with better outcomes in general) should be also considered.[39] In relation to statin exposure, non-users group may include former users of statins. Moreover, it is unknown whether statins were stopped, started or the dose was changed during the follow-up. The possibility of recall bias should be considered as the assessment of CVD comorbidities and other diseases was based on self-report alone. While some covariates adjusted for in our analysis may be potential mediators of statin use, they are also important risk factors for the clinical outcomes investigated in our analysis. The modified measurements for three components of the frailty score were used in this sample.

Participation in the CHAMP study was voluntary and clinical characteristics of participants may have differed to those of non-participants, which may have biased the sample. The study's generalisability may be limited as this sample comprised older men living in a defined geographical location. However, the response rate in the CHAMP study is similar to other comparable cohort studies of this type.[18] Moreover, the use of statins in this population (42.9%) was very similar to a random sample of older Australians aged ≥75 (43.0%). Finally, the findings of this study may not be applicable to older women.

In this prospective observational study, use of statins was not associated with a significantly increased risk of institutionalisation or death. However, in this sample, frail men were more likely to be institutionalised and die than non-frail men, independent of their statin exposure. Given the wide use of statins in older adults, regular clinical review of any observed or potential risks and benefits of statin therapy should be performed with older patients. Further longitudinal studies are warranted to confirm these associations in older women and in populations of older people across different settings. Finally, these findings call for pragmatic real-world trials specifically tailored for older frail people to examine the impact of statins on institutionalisation and other important clinical endpoints.

TABLES

Table 1. Characteristics of 1665 study participants according to baseline reported use of statins.

Characteristic[#]	**Total (n=1665)**	**Statin users (n=712; 42.8%)**	**Non-users (n=953; 57.2%)**	**P-value**

Age, mean (SD)	76.9 (5.5)	76.5 (5.1)	77.2 (5.7)	0.04
Age groups (years)				
<80	1184 (71.1)	533 (74.9)	651 (68.3)	
≥80	481 (28.9)	179 (25.1)	302 (31.7)	0.0004
Currently married	1255 (75.4)	550 (77.3)	705 (74.0)	0.13
Years of education, ≥7 years	1396 (84.7)	596 (84.5)	800 (84.8)	0.91
Country of birth				
Australia	831 (49.9)	356 (50.0)	475 (49.8)	
ESB immigrant	103 (6.2)	42 (5.9)	61 (6.4)	
Non-ESB immigrant	731 (43.9)	314 (44.1)	417 (43.8)	0.91
Alcohol consumption				
Lifelong non-drinker	144 (8.8)	53 (7.6)	91(9.8)	
Ex-drinker	239 (14.6)	105 (15.0)	134 (14.4)	
Safe drinker (1-21 drinks per week)	1127 (68.9)	492 (70.1)	635 (68.1)	
Harmful drinker (>21 drinks per week)	125 (7.7)	52 (7.4)	73 (7.8)	0.45

Smoking status				
Never smoker	620 (37.6)	240 (34.0)	380 (40.3)	
Previous smoker	929 (56.4)	431 (61.1)	498 (52.9)	
Current smoker	98 (6.0)	34 (4.8)	64 (6.8)	0.003
CVD diseases (≥2)	156 (9.5)	123 (17.4)	33 (3.5)	<0.0001
Self-reported comorbidities (≥2)	179 (10.9)	76 (10.8)	103 (10.9)	0.91
Polypharmacy (≥5)	618 (37.1)	412 (57.9)	206 (21.6)	<0.0001
Self-rated health, good or excellent	1153 (70.1)	463 (65.5)	690 (73.6)	0.0003
Visual acuity, low (<6/19)	71 (4.4)	18 (2.3)	53 (5.8)	0.002
BMI, mean (SD), kg/m^2	27.8 (4.0)	28.4 (3.7)	27.4 (4.2)	<0.0001
Depressive symptoms	240 (14.6)	100 (14.2)	140 (14.9)	0.70
Cognitive impairment (MCI or dementia)	205 (12.3)	76 (10.7)	129 (13.5)	0.08
ADL disability	134 (8.1)	50 (7.1)	84 (8.8)	0.19
IADL disability	674 (41.2)	318 (45.1)	356 (38.2)	0.005
Frail	147 (9.0)	53 (7.6)	94 (10.4)	0.08

Total cholesterol, mmol/L	4.6 (1.0)	4.0 (0.8)	5.0 (0.9)	<0.0001
HDL-cholesterol, mmol/L	1.4 (0.4)	1.4 (0.4)	1.5 (0.4)	0.0003
Triglycerides, mmol/L	1.4 (1.2)	1.4 (0.7)	1.4 (1.5)	0.06

Abbreviations: ADL, activities of daily living; BMI, body mass index; CVD, cardiovascular disease; ESB, English speaking background; HDL, high density lipoprotein; IADL, instrumental activities of daily living; MCI, mild cognitive impairment.

[#]Data are given as means (SD) or number (percentage) in the whole study population and within statin user and non-user groups. Percentages may not add up to 100% due to missing data.

Table 2. Association between reported statin use at baseline and institutionalisation and death

	Unadjusted HR (95%CI) (n=1665)		Adjusted HR (95%CI)[#] (n=1497)	
Categorisation of statin use	**Institutionalisation**	**Death**	**Institutionalisation**	**Death**
Statin exposure				
Non-users[*]	1.00	1.00	1.00	1.00
Users	0.90 (0.63, 1.27)	0.93 (0.75, 1.15)	1.60 (0.98, 2.63)	0.88 (0.66, 1.18)
Duration of statin use				
Non-users	1.00	1.00	1.00	1.00
0 - <4 years	1.10 (0.71, 1.68)	0.87 (0.65, 1.16)	1.73 (0.97, 3.10)	0.76 (0.53, 1.09)
≥4 years	0.73 (0.46, 1.17)	0.97 (0.75, 1.25)	1.48 (0.82, 2.68)	0.99 (0.71, 1.37)
Standardised daily dose[^]				
Non-users	1.00	1.00	1.00	1.00
Low	0.77 (0.47, 1.25)	0.98 (0.75, 1.29)	1.25 (0.69, 2.28)	0.92 (0.66, 1.29)
Medium	1.01 (0.61, 1.66)	0.97 (0.71, 1.33)	2.00 (1.02, 3.93)	0.95 (0.65, 1.40)
High	1.00 (0.55, 1.84)	0.73 (0.48, 1.12)	2.45 (1.12, 5.33)	0.65 (0.40, 1.07)

Abbreviations: CI, confidence intervals; HR, hazard ratio.

[#]Adjusted for age, education, marital status, alcohol use, smoking, body mass index, self-reported comorbidities, self-reported cardiovascular diseases, impaired vision, depression, cognitive impairment, functional status, self-rated health, polypharmacy and for total cholesterol, high density lipoprotein cholesterol and triglyceride concentrations.

[*]Non-users, the reference group.

[^]Standardised daily dose was defined as followed: one unit of equivalent dose was based on lipid-lowering effect of 10mg of atorvastatin (fluvastatin 80mg, lovastatin 40mg, pravastatin 40mg, simvastatin 2mg, rosuvastatin 5mg) (18,19). Low dose was defined as <2 standardised unit, medium dose as 2-4 standardised unit, and high dose as ≥4 standardised unit.

Table 3. Association between reported statin use at baseline and institutionalisation and death, adjusted for continuous and quintiles of propensity scores (n=1497)

	Adjusted HR (95%CI)[#]		Adjusted HR (95%CI)[*]	
Categorisation of statin use	**Institutionalisation**	**Death**	**Institutionalisation**	**Death**
Statin exposure				
Non-users[^]	1.00	1.00	1.00	1.00
Users	1.43 (0.87, 2.34)	0.82 (0.61, 1.10)	1.32 (0.81, 2.15)	0.81 (0.61, 1.08)
Duration of statin use				
Non-users	1.00	1.00	1.00	1.00
0 - <4	1.77 (1.01, 3.11)	0.74 (0.52, 1.06)	1.65 (0.95, 2.86)	0.73 (0.51, 1.04)
≥4	1.15 (0.64, 2.08)	0.88 (0.64, 1.22)	1.07 (0.59, 1.91)	0.87 (0.64, 1.20)
Standardised daily dose[†]				
Non-users	1.00	1.00	1.00	1.00
Low	1.17 (0.65, 2.13)	0.85 (0.61, 1.19)	1.10 (0.60, 1.99)	0.84 (0.60, 1.17)
Medium	1.73 (0.92, 3.27)	0.87 (0.60, 1.28)	1.57 (0.85, 2.93)	0.87 (0.60, 1.27)

High	1.71 (0.82, 3.57)	0.66 (0.41, 1.07)	1.56 (0.75, 3.24)	0.65 (0.41, 1.05)

Abbreviations: CI, confidence intervals; HR, hazard ratio.

#The HR estimated from Cox models, adjusted for continuous propensity score.

*The HR estimated from Cox models, adjusted for quintiles of propensity score.

^Non-users, the reference group.

†Standardised daily dose was defined as followed: one unit of equivalent dose was based on lipid-lowering effect of 10 mg of atorvastatin (fluvastatin 80mg, lovastatin 40mg, pravastatin 40mg, simvastatin 20mg, rosuvastatin 5mg) (18,19). Low dose was defined as <2 standardised unit, medium dose as 2-4 standardised unit, and high dose as ≥4 standardised unit.

Table 4. Association between reported statin use in frail versus non-frail men and institutionalisation and death

	Unadjusted HR (95%CI) (n=1631)	Adjusted HR (95%CI)[#] (n=1497)
Institutionalisation		
Non-frail participants not on statins[*]	1.00	1.00
Non-frail participants on statins	0.93 (0.60, 1.44)	1.43 (0.81, 2.51)
Frail participants not on statins	4.58 (2.82, 7.44)	2.07 (1.11, 3.86)
Frail participants on statins	5.47 (3.11, 9.61)	4.34 (2.02, 9.33)
Death		
Non-frail participants not on statins	1.00	1.00
Non-frail participants on statins	1.05 (0.83, 1.35)	0.90 (0.66, 1.23)
Frail participants not on statins	3.40 (2.49, 4.65)	1.53 (1.03, 2.28)
Frail participants on statins	3.01 (1.97, 4.61)	1.24 (0.71, 2.17)

Abbreviations: CI, confidence intervals; HR, hazard ratio.

#Adjusted for age, education, marital status, alcohol use, smoking, body mass index, self-reported comorbidities, self-reported cardiovascular diseases, impaired vision, depression, cognitive impairment, functional status, self-rated health, polypharmacy, total cholesterol, high density lipoprotein cholesterol and triglyceride concentrations.

*Non-users, the reference group.

FIGURES

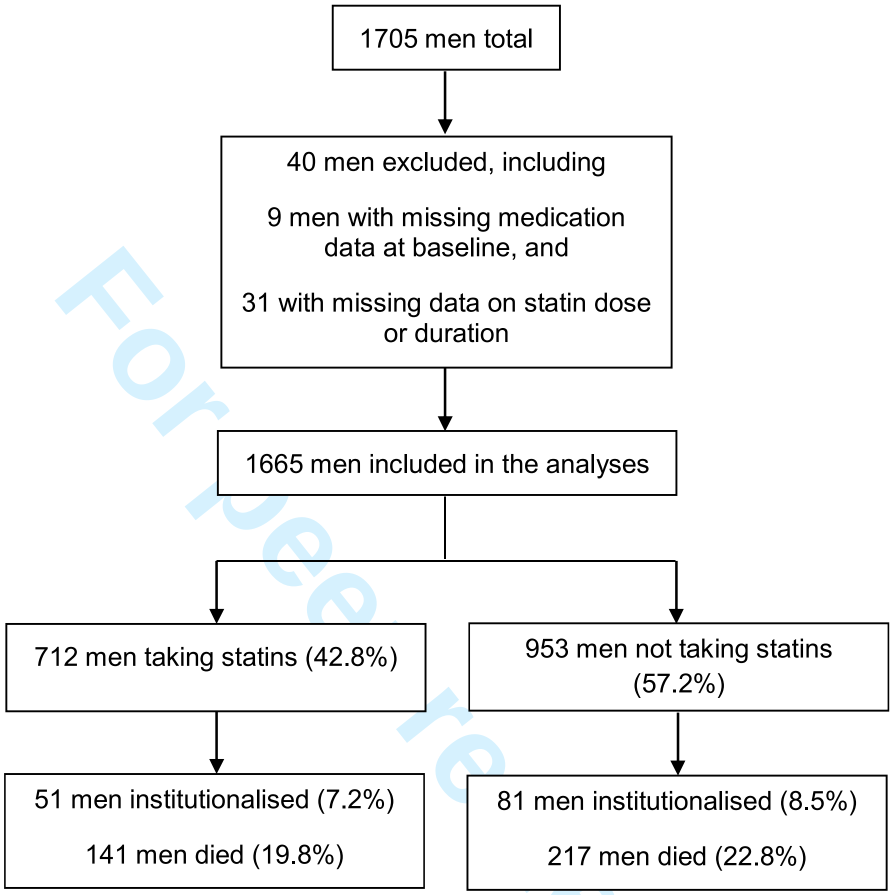
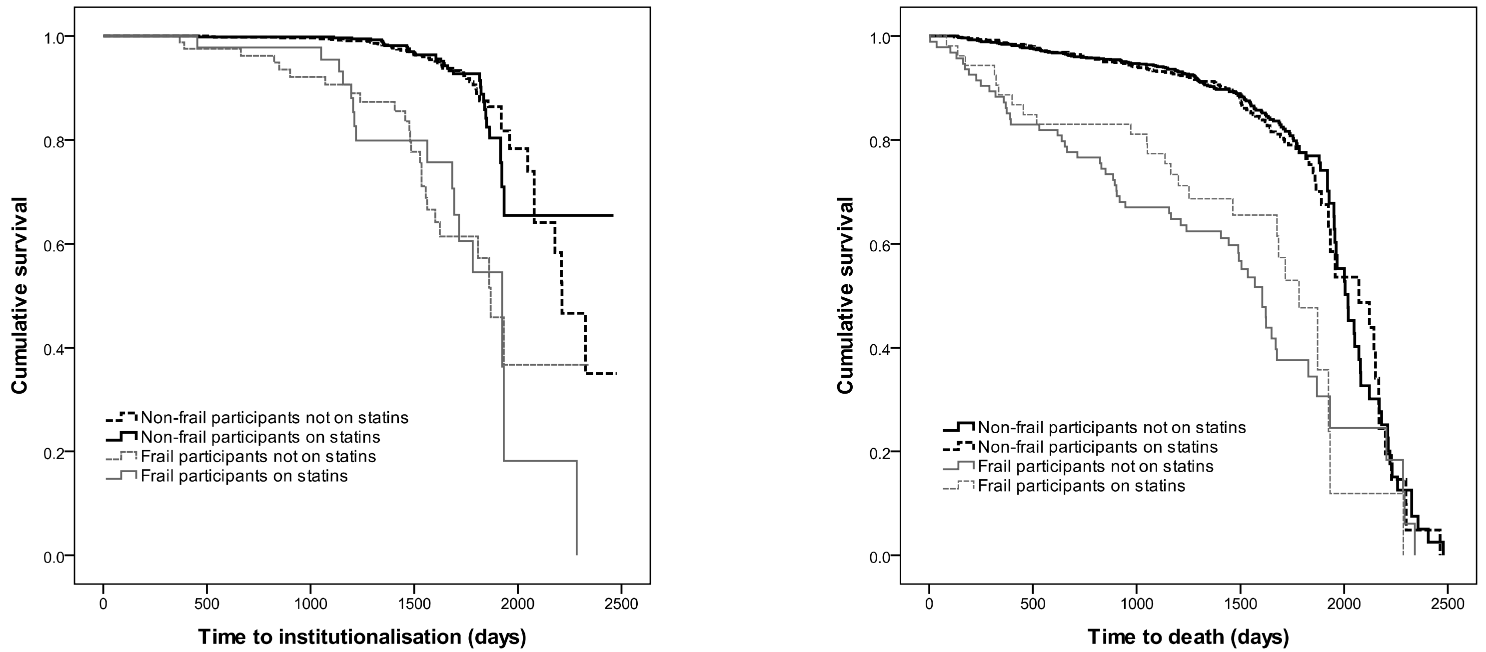


Figure 1. Flowchart for participants taking statins and institutionalisation and death in the CHAMP study



	Non-frail participants not on statins	Non-frail participants on statins	Frail participants not on statins	Frail participants on statins
N=1631	836	648	94	53
Institutionalised	50 (6.0%)	34 (5.3%)	25 (26.6%)	16 (30.2%)
Dead	149 (17.8)	115 (17.8%)	56 (59.6%)	25 (47.2%)

Figure 2. Kaplan-Meier survival curves for the time until institutionalisation (log-rank test, p<0.0001) and death (log-rank test, p<0.0001) by reported statin exposure and frailty.

Contributors

All authors contributed to the design of the study and co-wrote the manuscript. DG undertook the analysis and is the guarantor.

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Competing interests

None.

Ethical approval

The study was approved by the Sydney South West Area Health Service Human Research Ethics Committee Concord Repatriation General Hospital, Sydney, Australia.

Data sharing

No additional data available.

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Statin use and clinical outcomes in older men: a prospective population-based study

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ABSTRACT

Objective: The aim of this analysis was to investigate the relationship of statins with institutionalisation and death in older men living in the community, accounting for frailty.

Design: Prospective cohort study.

Setting: Community-dwelling men participating in the Concord Health and Ageing in Men Project, Sydney, Australia.

Participants: Men aged ≥70 years (n=1665).

Measurements: Data collected during baseline assessments and follow-up (maximum of 6.79 years) were obtained. Information regarding statin use was captured at baseline, between 2005 and 2007. Proportional hazards regression analysis was conducted to estimate the risk of institutionalisation and death according to statin use (exposure, duration and dose) and frailty status, with adjustment for socio-demographics, medical diagnosis, and other clinically relevant factors. A secondary analysis used propensity score matching to replicate covariate adjustment in regression models.

Results: At baseline, 43% of participants reported taking statins. Over 6.79 years of follow-up, 132 (7.9%) participants were institutionalised and 358 (21.5%) participants had died. In the adjusted models, baseline statin use was not statistically associated with increased risk of institutionalisation (hazard ratio [HR] =1.60; 95% confidence intervals [CI]: 0.98 to 2.63) or death (HR=0.88; 95%CI: 0.66 to 1.18). There was no significant association between duration or dose of statins used with either outcome. Propensity scoring yielded similar findings. Compared to non-frail participants not prescribed statins, the adjusted HR for institutionalisation for non-frail participants prescribed statins was 1.43 (0.81to 2.51), for frail participants not prescribed statins was 2.07 (1.11to 3.86) and for frail participants prescribed statins was 4.34 (2.02 to 9.33).

Conclusions: These data ~~imply no independent~~ suggest lack of significant association between statin use and institutionalisation or death in older men. These findings call for real-world trials specifically designed for older frail people to examine the impact of statins on clinical outcomes.

ARTICLE SUMMARY

Article focus

- Evidence from randomised trials support the benefits of statins in reducing cardiovascular morbidity and mortality.
- There is limited data in relation to statin use and clinical outcomes in representative populations of community-dwelling older people.

Key messages

- ~~The findings of~~In this prospective cohort study ~~imply no independent~~there was not significant association between statin use and institutionalisation or death in community-dwelling older men.
- Frail men were more likely to be institutionalised and die than non-frail men, independent of their statin exposure.
- Randomised trials ~~in frail and robust older people~~utilising operational frailty definitions with clinically relevant endpoints are required to inform therapy in this population.

Strengths and limitations of this study

- This is a ~~large~~ prospective cohort study of community-dwelling older men, with rich data sources.
- The study may have been underpowered to demonstrate the statistical significance in relation to statin use and institutionalisation.
- ~~The study sample comprised older men living in a defined geographical location, which may limit the study's generalisability.~~
- Observational studies of preventative medication users, including statins, are often biased by healthy user and healthy tolerator bias. ~~Although we have attempted to limit potential~~

~~confounding by adjusting our analysis for clinically important covariates, the possibility of confounding by indication and unmeasured confounders cannot be excluded.~~

INTRODUCTION

Statins or 3-hydroxy-3-methylglutaryl (HMG) coenzyme A reductase inhibitors are commonly used medicines in older people. ~~In a Canadian population aged ≥65 years, 42% were identified as statin users.~~ ~~A~~ In a recent Australian study ~~reported~~ 43% of community-dwelling people aged ≥75 years reported using statins.[1] The benefits of statins in relation to primary and secondary prevention of cardiovascular morbidity and mortality have been demonstrated in a number of randomised clinical trials (RCTs).[2 3] However, it is not clear how the findings of these trials translate to clinically significant outcomes in general populations of older people~~. This may be because~~ , as the representation and representativeness of older people in published RCTs of statins is generally poor.[4] Therefore, observational studies are often essential to elucidate the intended effects of medicines in this population.[5] Moreover, the benefit to harm ratio of medicines is altered in older adults due to co-morbid conditions, age-related physiological changes, increased risk of adverse drug reactions and multiple medicines.[6]

The pharmacological response to medicines is further altered when older individuals become frail.[7] Frailty is a geriatric syndrome associated with functional impairment and increased vulnerability to disease, disability, and mortality in older people.[8] Frail individuals are more likely to use more medicines,[9] and are at increased risk of adverse effects from medicines.[7] Conversely, frail older people are less likely to be recruited to and participate in RCTs.[7] There are currently limited data to guide prescribing to minimise medication-related harms in older people with geriatric syndromes including frailty. Moreover, evidence on clinically relevant outcomes of Drug-Geriatric Syndrome Interactions (DGSI) in older adults who have already developed a geriatric syndrome is limited.[10] It is unknown whether medicines do more good than harm in older adults with established geriatric syndromes.

There have been mixed findings across observational studies investigating the associations between statin use and geriatric syndromes and physical performance measures in older people. Statins have been associated with faster walking speed in patients with peripheral arterial or vascular disease.[11 12] In contrast, a recent study reported no association of statin use with mobility in older community-dwelling people.[13] In a study of community-dwelling older ~~disabled~~ women, current statin use was not associated with incident frailty over three years.[14] Statins in older people may increase the risk of both institutionalisation and death by causing myopathy or muscle damage.[15] Recent evidence also suggests that statins have adverse effects of energy and fatigue with exertion.[16] Statin-related myopathy is likely to have a greater impact in frail older adults with limited musculoskeletal reserve than in younger people who generally have more muscle mass and strength.

While the data from published RCTs and prospective studies indicate that statins reduce the incidence of cardiovascular events ~~and all-cause mortality~~,[17] there are still significant gaps in evidence on the safety of statins in a real-world setting. To our knowledge, no study has examined the association between the use of statins and institutionalisation in a representative population of older people, or in frail older people. Moreover, the evidence on the impact of interactions between statins and frailty (DGSI) on clinical outcomes in older people is yet to be established. The objectives of this study were to investigate the relationship of statin use, and of interactions between statins and frailty with institutionalisation and death in community-dwelling older men living in Sydney, Australia.

METHODS

Study population

Participants were community-dwelling men enrolled in the Concord Health and Ageing in Men Project (CHAMP), Sydney, Australia.[18] Eligible participants were ≥70 years and living in a specific study area. The only exclusion criterion was living in a residential aged care facility (RACF). The Electoral Roll was chosen as the sampling frame for the study. In Australia, registration on the Electoral Roll is compulsory and regularly updated, making it a suitable population-wide sampling frame. Men were recruited during 2005-2007. Of the 2815 eligible men contacted, 1511 (53.7%) participated in the study. An additional 194 (11.4%) men living in the study area heard about the study from friends or the local media and were recruited before receiving an invitation letter, giving a final sample of 1705 participants. Participants underwent baseline assessments which comprised self-completed study questionnaires and a clinical assessment that consisted of physical performance measures, neuropsychological testing, biological measures and medication inventory. Participants also agreed to be contacted every two years subsequently for follow-up assessment. After exclusion for missing data (n=40), a total of 1665 men were included in the analysis (Figure 1).

Medication assessment and classification of statin exposure

A medication inventory was conducted on each participant by trained personnel during the baseline clinic visit. Participants were instructed to bring all prescription and over-the-counter medications they were taking to the clinic visit for review. Participants were asked whether they had taken any ~~subsidised~~ prescription or non-prescription medications during the past month. Details of all medications and prescription pattern were recorded. Reported medicines were coded using the Iowa Drug Information Service code numbers.

Statin baseline exposure was defined using three approaches. We categorised participants as "statin users" versus "non-users". Data on the duration of statin use (years) were obtained and participants were dichotomised at the upper quartile ~~(~~≤(< ~~3~~ 4 versus ≥4). Statin users were characterised using the units of equivalent dose, indicating potency for lipid-lowering effect from clinical trials.[19 20] The daily dose of each statin was converted to an equivalent statin dose based on a lipid-lowering effect of 10mg of atorvastatin (equivalent to 5mg of rosuvastatin, 20mg of simvastatin, 40mg of lovastatin, 40mg of pravastatin, and 80mg of fluvastatin). Statin users were grouped into three categories, based on the data distribution, as receiving a low (equivalent dose < 2), medium (equivalent dose 2-4), and high (equivalent dose ≥4) statin dose.

Study outcomes

Data on institutionalisation and death were regularly updated by telephone contact with the participants or their nominated contact person at 4-monthly intervals. Men who were not contactable by telephone were sent letters at four monthly intervals. Institutionalisation was defined as entry into a nursing home facility or hostel at any time during the follow-up period of 6.79 years (average 4.0 years). In Australia, there are two main forms of RACFs: low-level care facilities (hostels) and high-level care facilities (nursing homes). Self-care retirement villages are not considered to be RACFs and residents are not considered "institutionalised". Moreover, institutionalisation in Australia is nearly always permanent rather than short-term admission for rehabilitative care after surgery or medical illness. For death outcome, if men withdrew from the study but agreed to passive follow up, the New South Wales *Registry of Births, Deaths and Marriages* was contacted to ascertain any deaths. Follow-up began at the baseline assessment and ended on the date of death or the end of the study period. For withdrawals, the end date was the date at which the contact with the death registry was made.

Covariates

Data on clinically relevant covariates that may influence the association between statin use and outcomes were obtained.[13 14] Demographic variables included age, education, and marital status. Data on country of birth were obtained and participants were categorised as Australian-born, overseas-born from an English-Speaking background (ESB), and overseas-born from a non-ESB. For those who consumed at least 12 alcoholic drinks in the past year, the frequency and quantity of alcohol consumption was assessed, and men were categorised as safe drinkers (1-21 alcoholic drinks per week) or harmful drinkers (>21 alcoholic drinks per week). Participants who were current non-drinkers were characterised as either "lifelong abstainers" or "ex-drinkers". Tobacco smoking status (allocated as "never smoker", "ex-smoker" or "current smoker") was also assessed.

Data on the cardiovascular diseases (CVD) including hypertension, coronary artery disease or myocardial infarction, angina, and congestive heart failure were obtained~~, and~~. The number of CVD diseases was dichotomised at the upper quartile (≤1 versus ≥2). Other medical conditions included: diabetes, thyroid dysfunction, osteoporosis, Paget's disease, stroke, Parkinson's disease, epilepsy, intermittent claudication, chronic obstructive lung disease, liver disease, chronic kidney disease or renal failure, cancer (excluding non-melanoma skin cancers), or arthritis. The number of reported comorbidities was dichotomised at the upper quartile (≤1 versus ≥2). Data on body mass index (BMI; kg/m^2) was obtained. Multiple medication use or polypharmacy was defined as the use of ≥5 regular prescription medicines.[21] Corrected visual acuity was assessed using a Bailey-Lovie chart (<6/19 indicating poor vision).[22] Data on self-rated health were obtained and dichotomised into excellent/good versus fair/poor/very poor. Depressive symptoms were assessed with the 15-item Geriatric Depression Scale (≥ 5 indicative of depressive symptoms).[23] Blood samples were drawn after overnight fasting. Total cholesterol, high density lipoprotein (HDL) cholesterol, and triglyceride concentrations were obtained and analysed as continuous variables.

All participants were screened for cognitive impairment, and those who tested positive underwent full neuropsychological assessment. Participants were classified as cognitively impaired if they were diagnosed with either dementia or mild cognitive impairment.[24] Functional status was measured with Activities of Daily Living (ADL) and Instrumental Activities of Daily (IADL) scales. Disability in ADL and IADL was defined as needing help with ≥1 activities.[25 26] Frailty in this population, described in detail elsewhere[27 28] was defined according to the criteria used in the Cardiovascular Health Study (CHS): weight loss/shrinking, weakness, exhaustion, slowness and low activity.[8] For the weakness and slowness components, the same criteria as in the CHS were applied. Adapted criteria were used for weight loss, exhaustion and low activity as the exact measurements used in the CHS were not available in this study.[27 28] Participants were considered *frail* if they had three or more frailty criteria, intermediate (*pre-frail*) with one or two criteria and robust (*not-frail*) without any criteria.

Statistical Analysis

Data are summarised as means (standard deviations) or counts (proportions). Differences in baseline characteristics between statin users and non-users were compared using the non-parametric or χ^2-tests as appropriate. Univariate analyses of the association between the various study measures and outcomes were conducted using Log-rank tests and examination of survival curves. Tests for linear trends were performed for continuous variables to determine the linearity of their relationship with institutionalisation and death, and to determine whether to enter these variables into models as continuous or categorical variables. The appropriate parameterisation of continuous variables as either categorical or continuous was also confirmed in the final model by using Akaike's Information Criterion (AIC). Univariate Cox regressions were conducted to determine the unadjusted hazard ratios (HR) with 95% confidence intervals (CI) for the effects of statins on institutionalisation and death. We then conducted the Cox proportional hazards regression models for the effects of statins on institutionalisation and death, adjusted for all potential confounding factors at baseline including age, education, marital status, alcohol use, smoking, BMI, self-reported comorbidities, self-reported cardiovascular diseases, impaired vision, depression, cognitive impairment, functional status, self-rated health, polypharmacy, total cholesterol, high density lipoprotein cholesterol and triglyceride concentrations. These analyses were performed for all different categorises of statin exposure.

The propensity score analysis was performed to minimize the effects of covariates in the evaluation of the association between statin use and institutionalisation and death.[29] Participant-specific propensity scores were estimated from a logistic regression model to predict the probability of statin prescription. All covariates were considered in the logistic regression model. The association between statins and institutionalisation and death was evaluated in Cox regressions models after adjusting for the estimated propensity score as a continuous and stratified (grouped into quintile) variable. Moreover, as older individuals with geriatric syndromes may have higher risk for either institutionalisation or death we conducted subgroup analysis. We stratified participants based on frailty status and statin use as *robust* or *pre-frail not on statins*; *robust* or *pre-frail on statins*; *frail not on statins* and *frail on statins*. Robust or pre-frail participants are referred as "non-frail" in the analysis. We also tested for interaction to assess whether statin effects differed in frail and non-frail men. Data were analysed using SAS version 9.3 (SAS Institute Inc., Cary, North Carolina). The Kaplan-Meier survival curves were generated using SPSS software version 19.0 (SPPS Inc, Chicago, Illinois).

RESULTS

The baseline characteristics according to statin use are presented in Table 1. The mean (SD) age of participants was 79.6 (5.5) years. At baseline, 743 (42.9%) participants were identified as taking a statin. Statin users were younger (p=0.04), had more CVD comorbidities (p<0.0001), used more medications (p<0.0001), had higher BMI (p<0.0001), and were less likely to report *good* or *excellent health* (p=0.003).In this population, 17% of participants reported taking statins for ~~≤3~~<4 years, and 26% for ≥4 years. In relation to the statin dose, 17% were taking low statin doses, 15% medium doses and 10% high statin doses. Over 6.79 years of follow-up, 132 (7.9%) participants were institutionalised and 358 (21.5%) participants had died. Figure 2 shows the Kaplan-Meier survival curves for institutionalisation and death according to reported statin exposure and frailty status at baseline. There was a significant difference between the groups in time to institutionalisation or death.

Table 2 summarises the results of the Cox regression models. In the adjusted models, baseline use of statins was not significantly associated with increased risks of institutionalisation (HR=1.60; 95%CI: 0.98 to 2.63) or death (HR=0.88; 95%CI: 0.66 to 1.18). Medium (HR=2.00; 95%CI: 1.02 to 3.93) and high (HR=2.45; 95%CI: 1.12 to 5.33) dose statin users were significantly more likely to be institutionalised when compared to those not taking statins. There was no association between the duration or dose of statins and death. The propensity score adjusted HR were not significantly altered apart from the association of statin doses with institutionalisation (table 3). In the propensity score adjusted models, current use of statins was not significantly associated with institutionalisation (HR=1.43; 95%CI: 0.87 to 2.34) or death (HR=0.82; 95%CI: 0.61to 1.10). Medium or high dose statin use was not significantly associated with a higher risk of institutionalisation compared to non-users.

The HRs for institutionalisation and death in frail versus non-frail men according to statin use are presented in Table 4. Using non-frail men who were not taking statins as the reference group at baseline, non-frail men prescribed statins had an adjusted HR of 1.43 (95%CI: 0.81 to 2.51) for institutionalisation, frail participants not taking statins had an adjusted HR of 2.07 (95%CI: 1.11to 3.86) and frail participants prescribed statins had a HR of 4.34 (95%CI: 2.02 to 9.33) for institutionalisation. Frail participants prescribed statins had a HR of 1.24 (95%CI: 0.71to 2.17) for death compared to non-frail participants not prescribed statins. However, among men not using statins, frail participants had a HR of 1.53 (95%CI: 1.03 to 2.28) for mortality compared to non-frail participants. In the adjusted models, there was no significant interaction between frailty and statin use with respect to institutionalisation (p=0.40) or mortality (p=0.73).

DISCUSSION

The objective of this cohort analysis was to evaluate the relationship between statins and two clinically important outcomes, institutionalisation and death in older men, accounting for frailty. The main finding of this prospective observational study of community-dwelling older men is the lack of independent association between the use of statins and institutionalisation or death. However, in this population, frailty was associated with higher risks of institutionalisation and death. Frail men were approximately two times more likely to be institutionalised and die over 6.8 years of follow-up compared to non-frail men, regardless of their medication exposure.

The prevalence of statin use in this population is comparable to recent studies[1 30] but much higher than that reported in studies of older people recruited in 1990s. In a study of older disabled women in the US, recruited during 1993-1998,[14] the prevalence of statin use was 8.4% compared to 12.9% in a community-dwelling sample of older people enrolled in the Health Ageing and Body Composition study during 1997-1998.[13] There are no studies conducted in older people that have investigated the association of statin use with institutionalisation. Some studies have showed that statins improve physical function, walking speed [11] but do not lower risk of incident frailty over 3 years.[14] Better performance on functional measures is protective against institutionalisation and death.[31 32] In our study, statin users had a hazard ratio of 1.60 (95% CI: 0.98 to 2.63) for increased risk of institutionalisation. Interestingly, high dose statin users had a hazard ratio of 2.45 (95% CI: 1.12 to 5.33) for increased risk of institutionalisation. However, this association was not significant in the propensity score adjusted model. Future studies conducted in larger populations are needed to investigate associations between statins and institutionalisation in older people. In relation to statins and mortality, among older people with diabetes living in the community, statin use has been associated with reduced risk of cardiovascular and all-cause mortality.[33] In contrast, the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial data demonstrates benefits in reducing the risks of coronary diseases, however there are no benefits in overall mortality.[34]

Moreover, frailty has been associated with an increased risk of institutionalisation[35] and death.[36] In this sample, frail men were more likely to be institutionalised and die than non-frail men, irrespective of their statin exposure. Even though there was no significant interaction between statin use and frailty on institutionalisation rates, frail men using statins had twice the risk of institutionalisation as frail men not using statins. These findings suggest that statins in frail older men may not reduce the risk of institutionalisation or death. Studies with larger number of frail participants are needed to estimate the risks of statins in frail older people.

There are several strengths of this study including the prospective design, good quality medication and outcome data, and adjustment for a number of covariates related to the risk of institutionalisation and death. A careful and systematic medication inventory was performed by checking all medications brought in by the men during a clinic visit. Frailty was ascertained using the validated scale.[37] We also performed sensitivity analysis including propensity score analysis and stratification of statin users according to their frailty status. While there are different propensity score models that can be used to balance measured covariates, the covariate propensity score adjustment has the best performance for estimating relative risks.[38]

However, there are important limitations to this study. The possibility of confounding by indication and unmeasured confounders needs to be acknowledged, as with any other observational study. Participants with CVDs would be more likely to be prescribed statins and among those with CVDs, those with more CVDs and more severe CVDs would be even more likely to be prescribed statins. In addition, participants adherent to treatment are likely to do better, which is hard to capture. These characteristics may have over or under estimated the HRs. The implications of healthy user bias (eg. unhealthy individuals will be less likely to use statins, which may indicate benefits of statins in observational studies) and healthy tolerator bias (eg. adherence to preventative drugs including statins is associated with better outcomes in general) should be also considered.[39] In relation to statin exposure, non-users group may include former users of statins. Moreover, it is unknown whether statins were stopped, started or the dose was changed during the follow-up. The possibility of recall bias should be considered as the assessment of CVD comorbidities and other diseases was based on self-report alone. While some covariates adjusted for in our analysis may be potential mediators of statin use, they are also important risk factors for the clinical outcomes investigated in our analysis. The modified measurements for three components of the frailty score were used in this sample.

Participation in the CHAMP study was voluntary and clinical characteristics of participants may have differed to those of non-participants, which may have biased the sample. The study's generalisability may be limited as this sample comprised older men living in a defined geographical location. However, the response rate in the CHAMP study is similar to other comparable cohort studies of this type.[18] Moreover, the use of statins in this population (42.9%) was very similar to a random sample of older Australians aged ≥75 (43.0%). Finally, the findings of this study may not be applicable to older women.

In this prospective observational study, use of statins was not associated with a significantly increased risk of institutionalisation or death. However, in this sample, frail men were more likely to be institutionalised and die than non-frail men, independent of their statin exposure. Given the wide use of statins in older adults, regular clinical review of any observed or potential risks and benefits of statin therapy should be performed with older patients. Further longitudinal studies are warranted to confirm these associations in older women and in populations of older people across different settings. Finally, these findings call for pragmatic real-world trials specifically tailored for older frail people to examine the impact of statins on institutionalisation and other important clinical endpoints.

TABLES

Table 1. Characteristics of 1665 study participants according to baseline reported use of statins.

Characteristic[#]	Total (n=1665)	Statin users (n=712; 42.8%)	Non-users (n=953; 57.2%)	P-value
Age, mean (SD)	76.9 (5.5)	76.5 (5.1)	77.2 (5.7)	0.04
Age groups (years)				
<80	1184 (71.1)	533 (74.9)	651 (68.3)	
≥80	481 (28.9)	179 (25.1)	302 (31.7)	0.0004
Currently married	1255 (75.4)	550 (77.3)	705 (74.0)	0.13
Years of education, ≥7 years	1396 (84.7)	596 (84.5)	800 (84.8)	0.91
Country of birth				
Australia	831 (49.9)	356 (50.0)	475 (49.8)	
ESB immigrant	103 (6.2)	42 (5.9)	61 (6.4)	
Non-ESB immigrant	731 (43.9)	314 (44.1)	417 (43.8)	0.91
Alcohol consumption				

Lifelong non-drinker	144 (8.8)	53 (7.6)	91(9.8)	
Ex-drinker	239 (14.6)	105 (15.0)	134 (14.4)	
Safe drinker (1-21 drinks per week)	1127 (68.9)	492 (70.1)	635 (68.1)	
Harmful drinker (>21 drinks per week)	125 (7.7)	52 (7.4)	73 (7.8)	0.45
Smoking status				
Never smoker	620 (37.6)	240 (34.0)	380 (40.3)	
Previous smoker	929 (56.4)	431 (61.1)	498 (52.9)	
Current smoker	98 (6.0)	34 (4.8)	64 (6.8)	0.003
CVD diseases (≥2)	156 (9.5)	123 (17.4)	33 (3.5)	<0.0001
Self-reported comorbidities (≥2)	179 (10.9)	76 (10.8)	103 (10.9)	0.91
Polypharmacy (≥5)	618 (37.1)	412 (57.9)	206 (21.6)	<0.0001
Self-rated health, good or excellent	1153 (70.1)	463 (65.5)	690 (73.6)	0.0003
Visual acuity, low (<6/19)	71 (4.4)	18 (2.3)	53 (5.8)	0.002
BMI, mean (SD), kg/m^2	27.8 (4.0)	28.4 (3.7)	27.4 (4.2)	<0.0001
Depressive symptoms	240 (14.6)	100 (14.2)	140 (14.9)	0.70

Cognitive impairment (MCI or dementia)	205 (12.3)	76 (10.7)	129 (13.5)	0.08
ADL disability	134 (8.1)	50 (7.1)	84 (8.8)	0.19
IADL disability	674 (41.2)	318 (45.1)	356 (38.2)	0.005
Frail	147 (9.0)	53 (7.6)	94 (10.4)	0.08
Total cholesterol, mmol/L	4.6 (1.0)	4.0 (0.8)	5.0 (0.9)	<0.0001
HDL-cholesterol, mmol/L	1.4 (0.4)	1.4 (0.4)	1.5 (0.4)	0.0003
Triglycerides, mmol/L	1.4 (1.2)	1.4 (0.7)	1.4 (1.5)	0.06

Abbreviations: ADL, activities of daily living; BMI, body mass index; CVD, cardiovascular disease; ESB, English speaking background; HDL, high density lipoprotein; IADL, instrumental activities of daily living; MCI, mild cognitive impairment.

[#]Data are given as means (SD) or number (percentage) in the whole study population and within statin user and non-user groups. Percentages may not add up to 100% due to missing data.

Table 2. Association between reported statin use at baseline and institutionalisation and death

	Unadjusted HR (95%CI) (n=1665)		Adjusted HR (95%CI)[#] (n=1497)	
Categorisation of statin use	**Institutionalisation**	**Death**	**Institutionalisation**	**Death**
Statin exposure				
Non-users[*]	1.00	1.00	1.00	1.00
Users	0.90 (0.63, 1.27)	0.93 (0.75, 1.15)	1.60 (0.98, 2.63)	0.88 (0.66, 1.18)
Duration of statin use				
Non-users	1.00	1.00	1.00	1.00
0 - ~~≤3~~<4 years	1.10 (0.71, 1.68)	0.87 (0.65, 1.16)	1.73 (0.97, 3.10)	0.76 (0.53, 1.09)
≥4 years	0.73 (0.46, 1.17)	0.97 (0.75, 1.25)	1.48 (0.82, 2.68)	0.99 (0.71, 1.37)
Standardised daily dose[^]				
Non-users	1.00	1.00	1.00	1.00
Low	0.77 (0.47, 1.25)	0.98 (0.75, 1.29)	1.25 (0.69, 2.28)	0.92 (0.66, 1.29)
Medium	1.01 (0.61, 1.66)	0.97 (0.71, 1.33)	2.00 (1.02, 3.93)	0.95 (0.65, 1.40)
High	1.00 (0.55, 1.84)	0.73 (0.48, 1.12)	2.45 (1.12, 5.33)	0.65 (0.40, 1.07)

Abbreviations: CI, confidence intervals; HR, hazard ratio.

#Adjusted for age, education, marital status, alcohol use, smoking, body mass index, self-reported comorbidities, self-reported cardiovascular diseases, impaired vision, depression, cognitive impairment, functional status, self-rated health, polypharmacy and for total cholesterol, high density lipoprotein cholesterol and triglyceride concentrations.

*Non-users, the reference group.

^Standardised daily dose was defined as followed: one unit of equivalent dose was based on lipid-lowering effect of 10mg of atorvastatin (fluvastatin 80mg, lovastatin 40mg, pravastatin 40mg, simvastatin 2mg, rosuvastatin 5mg) (18,19). Low dose was defined as <2 standardised unit, medium dose as 2-4 standardised unit, and high dose as ≥4 standardised unit.

Table 3. Association between reported statin use at baseline and institutionalisation and death, adjusted for continuous and quintiles of propensity scores (n=1497)

	Adjusted HR (95%CI)[#]		**Adjusted HR (95%CI)[*]**	
Categorisation of statin use	**Institutionalisation**	**Death**	**Institutionalisation**	**Death**
Statin exposure				
Non-users[^]	1.00	1.00	1.00	1.00
Users	1.43 (0.87, 2.34)	0.82 (0.61, 1.10)	1.32 (0.81, 2.15)	0.81 (0.61, 1.08)
Duration of statin use				
Non-users	1.00	1.00	1.00	1.00
0 - ~~≤~~<4~~3~~	1.77 (1.01, 3.11)	0.74 (0.52, 1.06)	1.65 (0.95, 2.86)	0.73 (0.51, 1.04)
≥4	1.15 (0.64, 2.08)	0.88 (0.64, 1.22)	1.07 (0.59, 1.91)	0.87 (0.64, 1.20)
Standardised daily dose[†]				
Non-users	1.00	1.00	1.00	1.00
Low	1.17 (0.65, 2.13)	0.85 (0.61, 1.19)	1.10 (0.60, 1.99)	0.84 (0.60, 1.17)
Medium	1.73 (0.92, 3.27)	0.87 (0.60, 1.28)	1.57 (0.85, 2.93)	0.87 (0.60, 1.27)

High	1.71 (0.82, 3.57)	0.66 (0.41, 1.07)	1.56 (0.75, 3.24)	0.65 (0.41, 1.05)

Abbreviations: CI, confidence intervals; HR, hazard ratio.

[#]The HR estimated from Cox models, adjusted for continuous propensity score.

[*]The HR estimated from Cox models, adjusted for quintiles of propensity score.

[^]Non-users, the reference group.

[†]Standardised daily dose was defined as followed: one unit of equivalent dose was based on lipid-lowering effect of 10 mg of atorvastatin (fluvastatin 80mg, lovastatin 40mg, pravastatin 40mg, simvastatin 20mg, rosuvastatin 5mg) (18,19). Low dose was defined as <2 standardised unit, medium dose as 2-4 standardised unit, and high dose as ≥4 standardised unit.

Table 4. Association between reported statin use in frail versus non-frail men and institutionalisation and death

	Unadjusted HR (95%CI) (n=1631)	**Adjusted HR (95%CI)[#] (n=1497)**
Institutionalisation		
Non-frail participants not on statins[*]	1.00	1.00
Non-frail participants on statins	0.93 (0.60, 1.44)	1.43 (0.81, 2.51)
Frail participants not on statins	4.58 (2.82, 7.44)	2.07 (1.11, 3.86)
Frail participants on statins	5.47 (3.11, 9.61)	4.34 (2.02, 9.33)
Death		
Non-frail participants not on statins	1.00	1.00
Non-frail participants on statins	1.05 (0.83, 1.35)	0.90 (0.66, 1.23)
Frail participants not on statins	3.40 (2.49, 4.65)	1.53 (1.03, 2.28)
Frail participants on statins	3.01 (1.97, 4.61)	1.24 (0.71, 2.17)

Abbreviations: CI, confidence intervals; HR, hazard ratio.

#Adjusted for age, education, marital status, alcohol use, smoking, body mass index, self-reported comorbidities, self-reported cardiovascular diseases, impaired vision, depression, cognitive impairment, functional status, self-rated health, polypharmacy, total cholesterol, high density lipoprotein cholesterol and triglyceride concentrations.

*Non-users, the reference group.

FIGURES

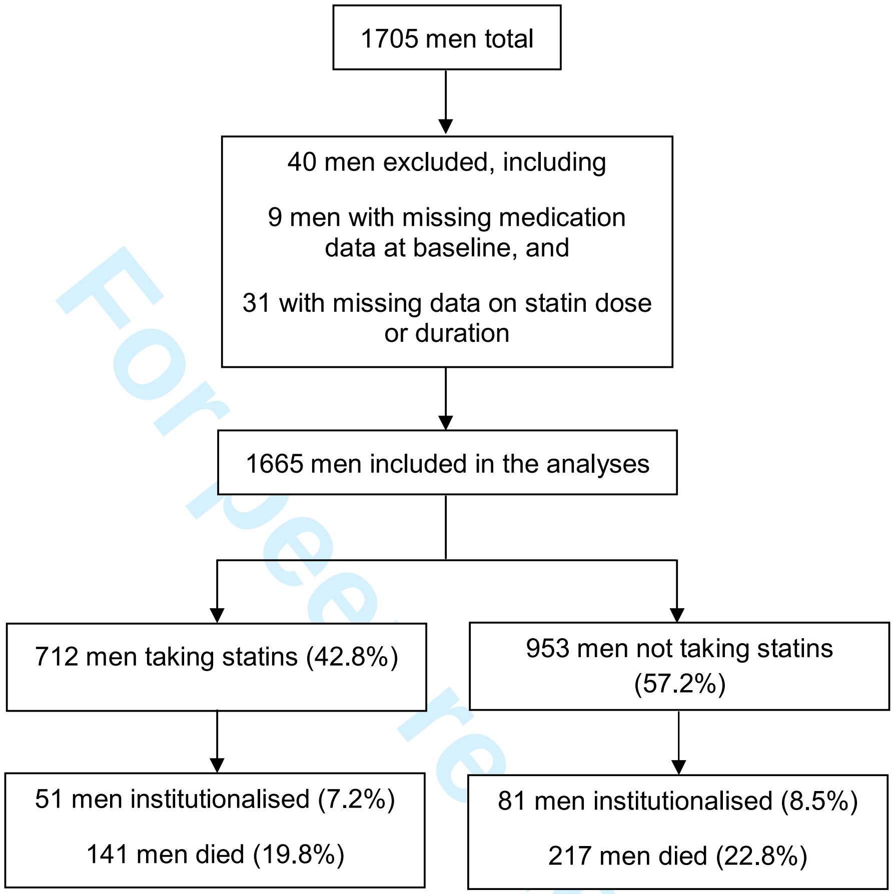
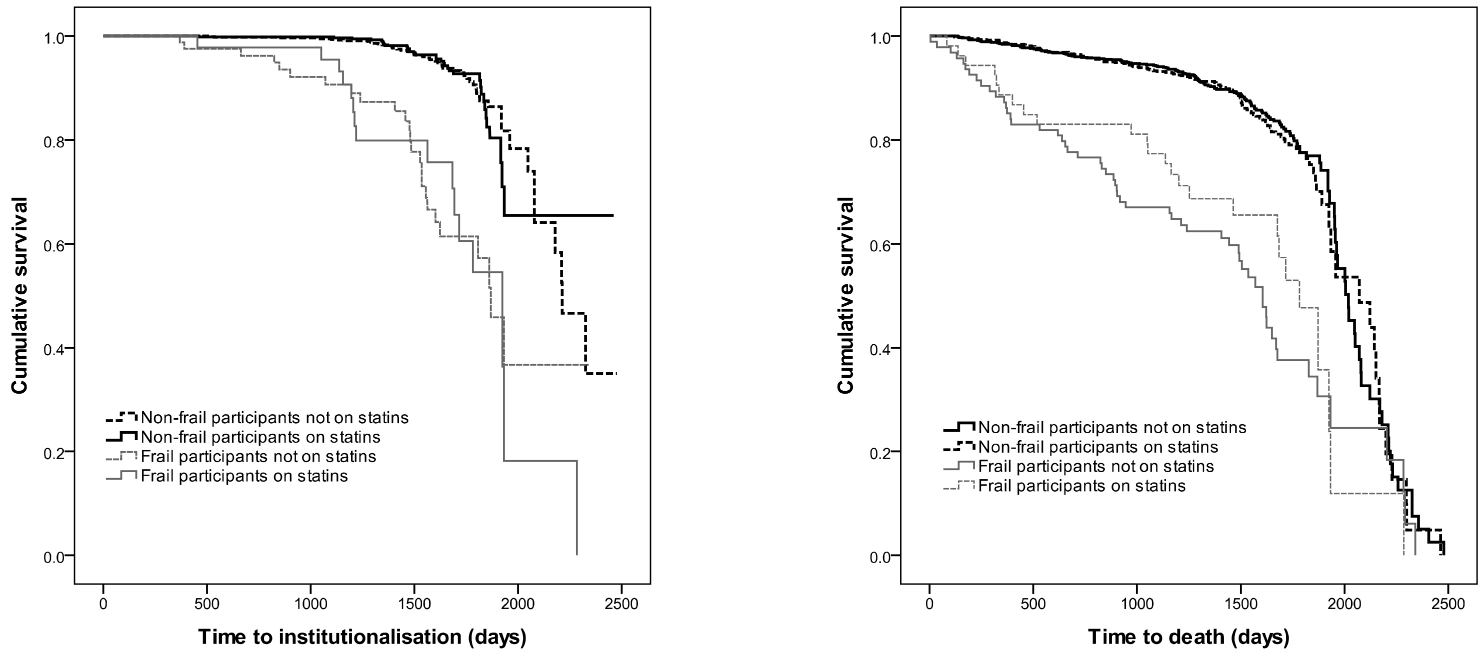


Figure 1. Flowchart for participants taking statins and institutionalisation and death in the CHAMP study



	Non-frail participants not on statins	Non-frail participants on statins	Frail participants not on statins	Frail participants on statins
N=1631	836	648	94	53
Institutionalised	50 (6.0%)	34 (5.3%)	25 (26.6%)	16 (30.2%)
Dead	149 (17.8)	115 (17.8%)	56 (59.6%)	25 (47.2%)

Figure 2. Kaplan-Meier survival curves for the time until institutionalisation (log-rank test, p<0.0001) and death (log-rank test, p<0.0001) by reported statin exposure and frailty.

Contributors

All authors contributed to the design of the study and co-wrote the manuscript. DG undertook the analysis and is the guarantor.

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Competing interests

None.

Ethical approval

The study was approved by the Sydney South West Area Health Service Human Research Ethics Committee Concord Repatriation General Hospital, Sydney, Australia.

Data sharing

No additional data available.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	8-9
Objectives	3	State specific objectives, including any prespecified hypotheses	9
Methods			
Study design	4	Present key elements of study design early in the paper	10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	10,11
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10-13
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*10-13*
Bias	9	Describe any efforts to address potential sources of bias	14
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10-13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	13-15
		(*b*) Describe any methods used to examine subgroups and interactions	14
		(*c*) Explain how missing data were addressed	10
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	14
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	16-17
		(b) Give reasons for non-participation at each stage	30
		(c) Consider use of a flow diagram	30
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	16
		(b) Indicate number of participants with missing data for each variable of interest	Tables 1-4
		(c) Summarise follow-up time (eg, average and total amount)	11, 16
Outcome data	15*	Report numbers of outcome events or summary measures over time	16, 30
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	16, 17
		(*b*) Report category boundaries when continuous variables were categorized	12, 13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Tables 3 and 4, pages 16, 17
Discussion			
Key results	18	Summarise key results with reference to study objectives	18
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	32

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.